Intensive care unit of the future: health informatics technologies for preventing critical illness brain injury in the ICU

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Contents

Overview

This document contains proposals for the development of the following health informatics systems with applications in the prevention of critical illness brain injury in intensive care units (ICU): (1) a clinical decision support system for sedation choice and management, (2) a patient-centric system for sleep efficacy improvement and care organization, (3) and a clinical decision support system for patient extubation.

The development of each proposal was based on:

- literature reviews of:
    - ICU technologies including sensing and treatment delivery modalities, their limitations, and use cases;
    - ICU health informatics systems and algorithms for knowledge creation based on sensing technologies; relevant health literature including cognitive impairment in the ICU and following ICU treatment, their causes, diagnosis, risk factors, treatments, and recovery trajectories;
- stakeholder analysis, needs assessments, preference elicitations, workflow analyses based on interviews with stakeholders and literature reviews;
- interviews with clinicians, intensivists, nurses, ICU survivors, scientists, and developers as well as their public testimonies and accounts present in the literature;
- critical care data analysis using public and proprietary datasets;
- market analysis of relevant sensing technologies and health informatics systems using sensor data offered by Philips (the primary stakeholder) and its competitors.

Each proposal includes selected key insights from the aforementioned analyses accompanied by descriptions of systems architecture, data flow diagrams, and graphical user interface prototypes. The described systems represent a subset of all considered technologies. Their selection was based on technical feasibility, potential impact, alignment with the primary stakeholder's core competencies and business strategy.

Introduction

What is Critical Illness Brain Injury (CIBI)?

Definition

The umbrella term "critical Illness brain injury" (CIBI) refers to a broad range of well-documented cognitive impairments frequently suffered by a large proportion of patients (up to 78%) following critical illness (Girard, Dittus, & Ely, 2016; Wilcox et al., 2013). Unlike dementia, CIBI has a sudden onset, which, in more severe cases, may be detected already in the ICU (Figure 1) (Girard et al., 2016).

Of note is the fact CIBI is present in patients across a spectrum of critical illnesses suggesting that its etiology may be, at least partially, independent of the original condition. Robust research demonstrates that some of CIBI's risk factors, e.g., unnecessarily prolonged sedation, can be reduced by modifying ICU treatment protocols providing a promising avenue for lowering CIBI's prevalence (J. Jackson & Ely, 2013; Kachmar, Irving, Connolly, & Curley, 2018).

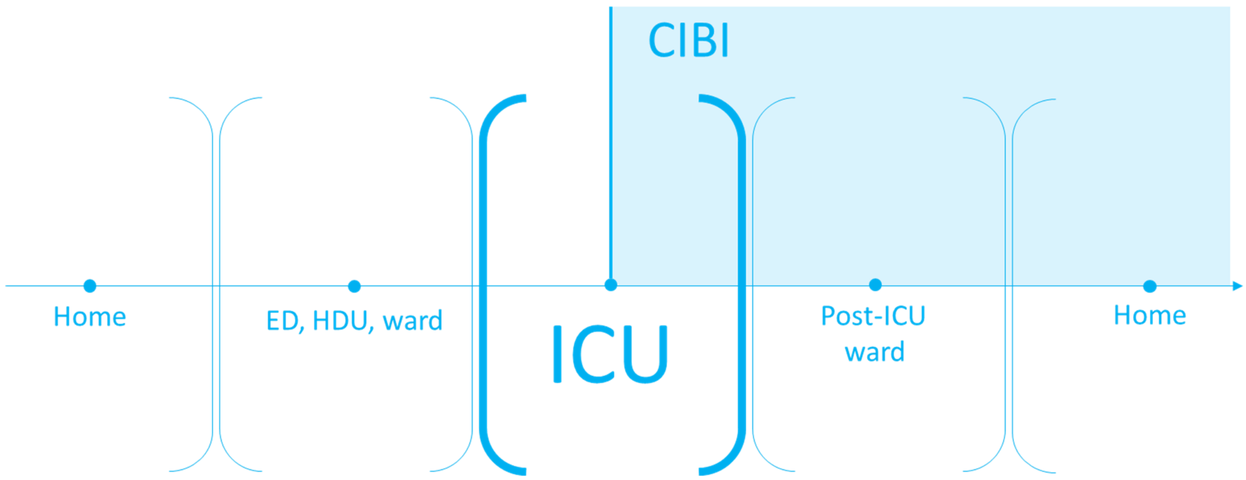

Figure 1. The onset of CIBI on the spectrum of care

Prevalence

Across multiple studies (for review see: Wilcox et al., 2013), reported prevalence of CIBI varies between 51% to 100% at discharge, 13% to 79% at three of six months following discharge, and 10% to 71% at one year following discharge from the ICU (Ambrosino, Bruletti, Scala, Porta, & Vitacca, 2002; Carlson & Huang, 2013; Guillamondegui et al., 2011; Hopkins et al., 2010; Hopkins, Weaver, Chan, & Orme, 2004; Hopkins et al., 2005; HOPKINS et al., 1999; J. C. Jackson et al., 2007, 2011, 2010, 2003; Jones, Griffiths, Slater, Benjamin, & Wilson, 2006; Larson, Weaver, & Hopkins, 2007; Sacanella et al., 2011; Suchyta, Jephson, & Hopkins, 2010; Sukantarat, Burgess, Williamson, & Brett, 2005; Tobar, …, & 2009, n.d.; Woon, Dunn, & Hopkins, 2012). As this research is still in its nascent phase, there are no established benchmarks for CIBI assessment, which might explain the width of the above ranges. While there is a dearth of relevant studies conducted outside of the US, a study conducted in South Korea, reported CIBI in 43.3% of ICU survivors (J. C. Jackson et al., 2011). Furthermore, a group of researchers found cognitive impairment to be present in 49.9% of survivors of Brazilian ICUs (de Azevedo et al., 2017). These two lone studies suggest that the high prevalence of CIBI might be not solely a US phenomenon.

Risk factors

There is strong evidence suggesting that sepsis (Iwashyna, Ely, Smith, & Langa, 2010; Semmler et al., 2013) and time spent in delirium are risk factors for CIBI (Elizabeth Wilcox et al., 2013). Research on the role of hypoxemia and hypotension in CIBI is inconclusive. For example, while the partial pressure of O2 in arterial blood was found to correlate with cognitive parameters (Mikkelsen et al., 2012), other studies did not detect such relationship (Guillamondegui et al., 2011). Preexisting depression, cognitive impairment, and sleep efficiency are good candidate risk factors, but current research on their role in CIBI is lacking. As adaptive cognitive stimulation plays a role in cognitive rehabilitation, it is conceivable that the lack of stimulation contributes to an increased risk of CIBI. Unfortunately, as of yet, no studies investigated this relationship.

Due to the largely preventable nature of delirium and its strong predictive power of CIBI, delirium's risk factors can be considered as indirect risk factors for CIBI. Those factors include: presence of APOE4 allele (W. E. Ely et al., 2007), smoking (>10 cigarettes per day), alcohol consumption (>3 units per day), certain sedative medication (mostly opiates and benzodiazepines), electrolyte disorders (Wang, Xu, Wei, Chang, & Xu, 2016), and sleep quality (for review of delirium's risk factors see: Arumugam et al., 2017).

Burden

Financial

According to the Society of Critical Care Medicine, US ICUs admit over 5.7 million patients every year (The Society of Critical Care Medicine, n.d.) with over 55,000 patients being in US ICUs at any day of the year (Gordon, Jackson, Ely, Burger, & Hopkins, 2004; Schmitz, Lantin, & White, 1998). As of 2010, there were between 103,900 and 91,669 ICU beds in the US constituting between 16.2% and 13.6% of all hospital beds. According to the same study, average ICU cost per day was $4,300, and total critical care costs reached $108 billion accounting for 13.2% of all hospital costs (Halpern & Pastores, 2015). In 2000, the median cost per ICU patient was between $25,000 and $35,000 (E. W. Ely, Baker, Evans, & Haponik, 2000). ICU stay is not the only driver of CIBI costs. Over 40% of ICU survivors need continuous medical care for over two years, and post-discharge costs constitute 28.9% of total costs (Cheung et al., 2006; Desai, Law, & Needham, 2011).

As delirium is present in up to 80% of ICU patients and is the strongest predictor of length of stay (Inouye et al., 1999) as well as a risk factor for CIBI (Elizabeth Wilcox et al., 2013), delirium prevention may lead to substantial savings; particularly for Accountable Care Organizations and Veterans Health Administration.

Currently, there is no research quantifying the cost of CIBI[1]. However, emerging research on the impact of acute brain dysfunction, i.e., delirium or coma, on healthcare costs demonstrated that patients suffering from acute brain dysfunction incurred costs of $238,726 during the first 30-day following discharge vs. $105,779 for a patient without that condition (Vasilevskis, Holtz, & Girard, 2015). As cognitive impairment, the core component of CIBI, leads to lower medication adherence and may decrease therapy adherence, CIBI most likely results in higher readmission rates (Alosco et al., 2012; Anderson & Birge, 2016; Cameron et al., 2010; Ketterer et al., 2016; Rogers, Bai, Lavin, & Anderson, 2017). Given increased readmission rates among delirious patients, CIBI patients may be more likely to return to the ICU after being discharged to a post-ICU ward (so-called "bounce-back") (Eide et al., 2016; Elsamadicy et al., 2017) further increasing costs of care. With our increasingly aging society, we may expect even more frequent use of intensive care units (Desai et al., 2011; Needham et al., 2005) resulting in an influx of CIBI patients and a surge in care costs. Therefore, solutions focused on prevention of CIBI and rapid rehabilitation will be an important driver of cost reduction. Additional research on the financial impact of CIBI on the healthcare system has the potential to not only meaningfully contribute to the existing body of knowledge, but also to unravel new market opportunities.

Non-financial

Patients with CIBI suffer from multiple cognitive impairments spanning long- and short-term memory, attention, executive function (e.g., cognitive inhibition, inhibitory control), processing speed, and visuospatial ability (Clancy, Edginton, Casarin, & Vizcaychipi, 2015; Elizabeth Wilcox et al., 2013; Hopkins & Brett, 2005; Hopkins & Jackson, 2006; Hopkins et al., 2005). Through its negative impact on cognitive and executive functions, CIBI is detrimental to functional status and psychological health resulting in

[1] An independent, leading expert in CIBI informally confirmed this gap in research.

lowered health-related quality of life (HRQOL) and difficulties in maintaining a job (Elizabeth Wilcox et al., 2013; Hopkins & Brett, 2005; Rothenhäusler, Ehrentraut, Stoll, Schelling, & Kapfhammer, 2001).

CIBI is only one part of a post-intensive care syndrome (PICS). PICS, in addition to cognitive impairments, also includes psychiatric and physical deficiencies which persist beyond discharge (de Azevedo et al., 2017). In 2012, 30 members of the Society of Critical Care Medicine published a report urging for research leading to a better understanding and amelioration of PICS (Needham et al., 2012). To maintain their presence in the ICU and beyond on the spectrum of care will require health technology vendors to focus on PICS in the near future.

Problem Statement

Given already high and continuously increasing prevalence of CIBI, its impact on patients' lives as well as enormous associated care costs, CIBI is likely to become one of the major challenges for healthcare systems around the world in the decades to come.

To address this issue, the focus of this research is on proposing how to improve HRQOL and to lower re-admission rates (at 30 days, 180 days, and 1 year following discharge) of ICU patients by creating financially sustainable health informatics solutions for the prevention of critical illness brain injury in the ICU that leverage the primary stakeholder's technological expertise.

Proposals

The following sections include literature reviews and proposals of health informatics technologies for preventing CIBI. Based on our informal interviews with clinicians (including intensivists) the proposed technologies are limited to those that are aligned with their preferences, i.e., are evidence-based, do not take control away from clinicians, and have a time-saving, efficiency-enhancing potential.

As outlined in the introduction, the key risk factors for CIBI are sepsis (Iwashyna, Ely, Smith, & Langa, 2010; Semmler et al., 2013) and time spent in delirium (Elizabeth Wilcox et al., 2013). There is not yet conclusive evidence on the role of hypoxemia and hypotension. However, a strong level of evidence suggests that risk factors for delirium, e.g., sleep quality and type of sedative used, constitute indirect risk factors for CIBI. Finally, candidate risk factors for CIBI include preexisting depression, cognitive impairment, and sleep efficiency (Figure 2).

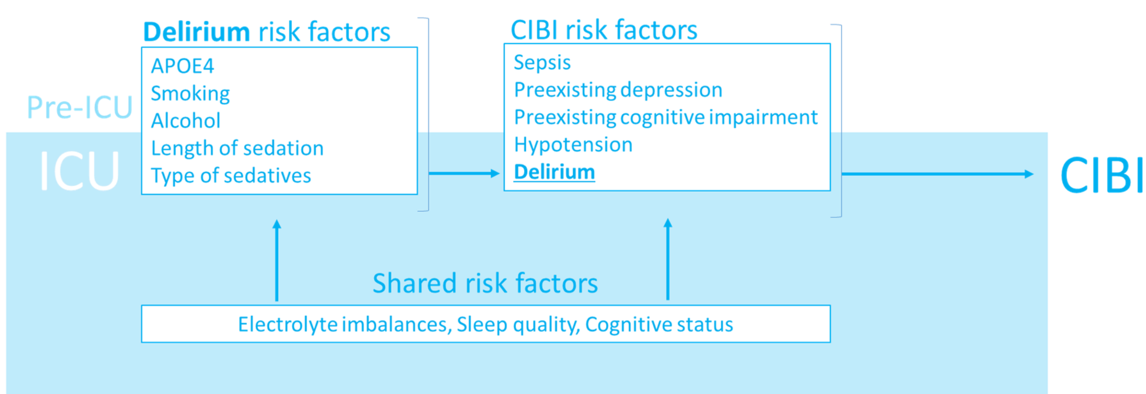

Figure 2. Direct and indirect risk factors for CIBI. Delirium risk factors are depicted as risk factors for CIBI.

Factors outside the blue area are usually measured before ICU admission and can be found in historical electronic health records. Conversely, items within the blue area are measured in the ICU; some of them, e.g., length of sedation, are partially under intensivists' control.

Currently, the ABCDEF bundle is the most comprehensive, evidence-based set of guidelines which can be used for targeting delirium and CIBI prevention (E. W. Ely, 2017; Marra, Ely, Pandharipande, & Patel, 2017). A subset of relevant ABCDEF's principles, outlined below, motivated and guided the selection and design of health technologies proposed in subsequent sections.

The ABCDEF bundle guidelines consist of:

A) "**A**ssessment, Prevention, Management of Pain,"
B) "**B**oth Spontaneous Awakening Trials and Spontaneous Breathing Trials,"
C) "**C**hoice of Sedation and Analgesia,"
D) "**D**elirium Assessment, Prevention, and Management,"
E) "**E**arly Mobility and Exercise,"
F) "**F**amily Engagement and Empowerment."

Analysis of available ICU technologies, the primary stakeholder's business focus and technological expertise, the strength of evidence, and potential impact on patients' health enabled narrowing down the space of viable solutions to CIBI and delirium prevention through 1) sedation and extubation decision support (guidelines B, C, D) and 2) improved sleep efficiency.

ICU technologies proposed in subsequent sections are not meant to comprehensive. Instead, they are to be integrated into a larger "ICU of the Future "clinical decision support system.

Clinical decision support for sedative choice

As confirmed during our informal interviews, high demands on intensivists' time and relatively low awareness of CIBI make careful, continuous assessment of CIBI risk challenging. At the same time, the strong predictive power of certain risk factors, e.g., sepsis, length of sedation, use of benzodiazepines, suggest the development of an accurate, real-time CIBI Risk Assessment Algorithm (CRAA) should be feasible. CRAA is intended to be embedded into a CDS to guide intensivists' sedative choice based on present and predicted CIBI risks.

Background

Sedative selection plays a key role in ICU care. Undersedated patients unnecessarily suffer from anxiety and pain leading to multiple negative outcomes including immunosuppression, hypercoagulability, hypermetabolism, acute agitation and dangerous self-extubation. Symmetrically, oversedation leads to delirium, coma, prolonged mechanical ventilation and ICU stay, and CIBI (Girard et al., 2016; Hughes, McGrane, & Pandharipande, 2012; Rowe & Fletcher, 2008). Based on prior research (Arroliga et al., 2005; Mehta, Syeda, Wiener, & Walkey, 2015), estimated at least 491 850 patients are sedated in the ICU every year.

Sedatives' impact on patients' health transcends sedation depth and includes changes in cardiovascular, kidney and liver function (Hughes et al., 2012; Rowe & Fletcher, 2008). In the context of CIBI prevention and psychological health, midazolam, is considered cognitively toxic (Hsu et al., 2015) and was demonstrated to dramatically increase the risk of delirium when compared with dexmedetomidine (OR: 2.47; 95% CI: 1.17–5.19) (Zhang, Chen, Ni, Zhang, & Fan, 2017). Use of another popular sedative, lorazepam, is associated with increased risk of PTSD and is an independent risk factor for transitioning into delirium (Girard et al., 2007; Pandharipande et al., 2006).

Sedative choice requires intensivists to consider multiple data sources about a given patient to carefully balance negative health outcomes with sedation's benefits. In a highly dynamic and stressful ICU environment making a complex decision is often challenging and results in suboptimal outcomes. Between 40% and 60% of patients are oversedated, and 10% - 30% are undersedated (D. L. Jackson, Proudfoot, Cann, & Walsh, 2009; Peitz, Balas, Olsen, Pun, & Ely, 2013).

Currently, in their sedative choice decisions, intensivists are encouraged to follow clinical guidelines. Unfortunately, adoption of those guidelines tends to be low (Chanques & Jaber, 2007; Egerod, Christensen, & Johansen, 2006) and algorithm-based guidelines are not always effective (Elliott, McKinley, Aitken, & Hendrikz, 2006). Existing clinical algorithms usually take the form of simplistic decision trees using relatively few decision criteria. It is conceivable that a computational, multiparameter model would outperform existing clinical guidelines.

At the moment, there exist no computational models to assist in sedation choice. Furthermore, no risk assessment algorithms for CIBI have been developed. Research thus far has focused on delirium only. In particular, significant effort was put into developing clinical algorithms to assist ICU personnel in detecting delirium using medical history and ICU-specific Confusion Assessment Method and Intensive Care Delirium Screening Checklist (Bergeron, Dubois, Dumont, Dial, & Skrobik, 2001; Hsieh, Ely, & Gong, 2013; Pisani et al., 2006).

Research on computational risk assessment for cognitive impairment in the ICU is relatively rare. Nevertheless, at least four research groups developed a couple of promising predictive models with applications to delirium and coma (Douglas et al., 2013; Marra et al., 2018; van den Boogaard et al., 2012, 2014). Furthermore, there exists a spectrum of risk prediction models for postoperative delirium, but those algorithms are not ICU-specific (Moon, Jin, Jin, & Lee, 2018; van Meenen, van Meenen, de Rooij, & ter Riet, 2014). Models referenced in this paragraph would serve a good starting point for creating an algorithm to assess the risk of developing cognitive impairment in the ICU.

Existing solutions

To the best of our knowledge, there exist no CDS systems for sedation choice.

Opportunities

The risk assessment algorithm's output is intended to serve as an input into a clinical decision support (CDS) tool to inform intensivists sedative selection. Figure 3 depicts the algorithm's risk predictions for each additional day of benzodiazepine use.

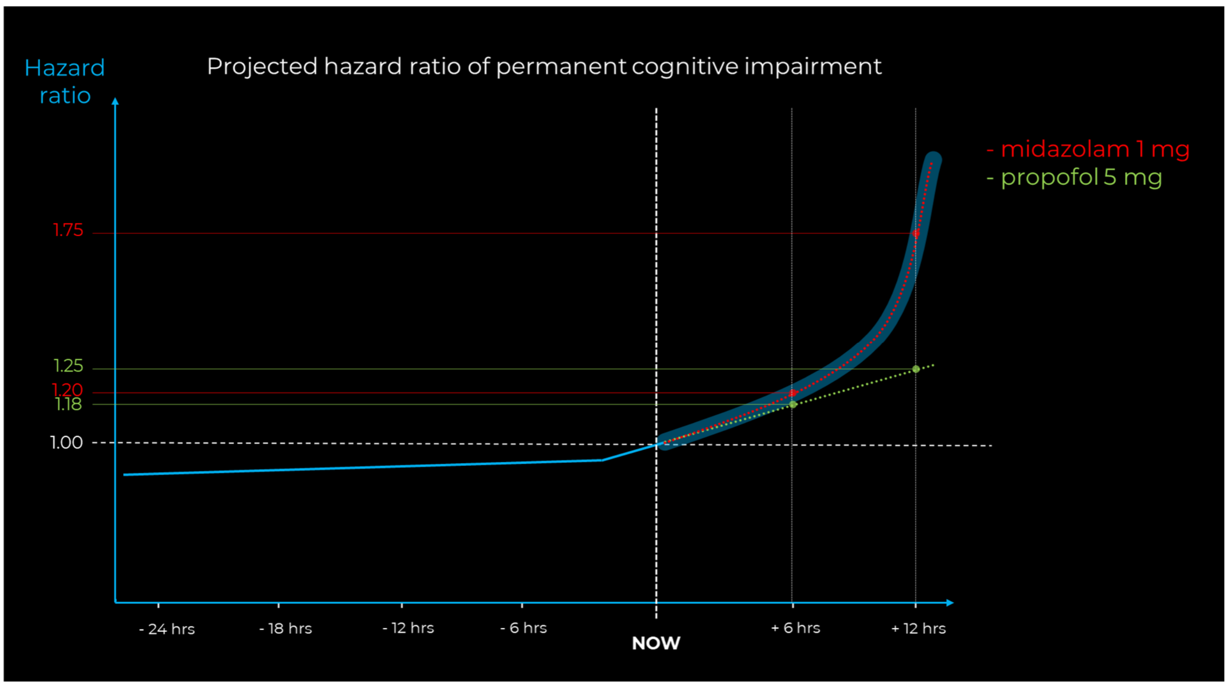

Figure 3. Example illustration of sedation CDS output based on CRAA.

Projections of hazard ratios indicate hazards of developing CIBI from exposure to a given sedative in references to continuing current treatment, i.e., not introducing the sedative at the indicated dose. Here, the CDS predicts that introducing midazolam 1 mg (benzodiazepine) will increase hazard ratio of CIBI by 0.75 while propofol 5 mg (not a benzodiazepine) will increase it by only 0.25. This insight informs intensivist's sedative selection.

Furthermore, based on individual responses to sedatives, e.g., captured by bispectral index (BIS)[2] monitors, the algorithm predicts and recommends the minimum effective dose for each individual patient for a given sedation level (Figure 4) to prevent oversedation.

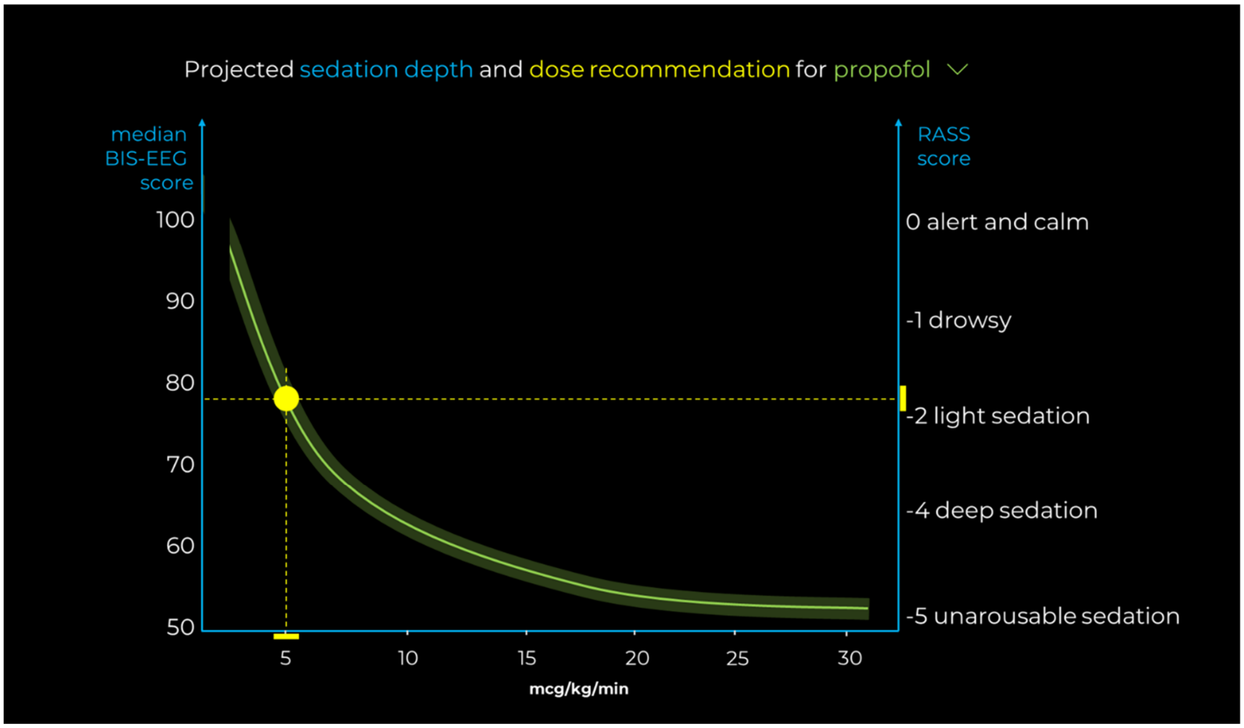

Figure 4. Example illustration of minimum effective dose recommendation.

Candidate inputs to the algorithm based on existing evidence and interviews with clinicians are as follows:

- Historical medical data from electronic health records:
    - sepsis episodes prior to current ICU stay,
    - preexisting depression,
    - preexisting cognitive impairment,
    - age, weight, BMI,
    - presence of APOE4,
    - number of cigarettes per day, number of alcoholic drinks per day,
    - electrolyte imbalances; especially hyponatremia and hypocalcemia (Wang et al., 2016; Zieschang et al., 2016),
    - medication history (including steroid use, liver and kidney function),
    - Acute Physiology And Chronic Health Evaluation (APACHE) IV score (Zimmerman, Kramer, McNair, & Malila, 2006);
- ICU, near real-time data, preferably as a time series:
    - sedation (what sedative was used, for how long, time of administration, dose),

[2] Bispectral index monitors translate electrical activity of the brain into single BIS values ranging from 0 to 99, where 0 indicates no brain activity and 99 indicates full awareness. BIS values are used as a continuous, objective measures of consciousness and sedation depth (Rowe & Fletcher, 2008).

- electrolyte data; especially hyponatremia and hypocalcemia (time, length, severity),
- hypotension (onset, levels),
- time spent in delirium (if any; onset, length),
- steroid use (what steroid was used, for how long, time of administration, dose),
- liver enzymes,
- kidney health parameters,
- cardiovascular health biomarkers,
- sedation depth (preferably quantified using a bispectral index or a broader range of EEG features),
- sleep quality (if possible to assess),
- cognitive status (in the ICU; if possible to assess),
- sepsis developed during current ICU stay,
- sedative treatment options.

Integration of a bispectral index (BIS) into the CDS provides a unique opportunity to further increase the utility of the proposed system. The sedative response is highly patient-specific. For this reason, assessment of sedation depth is a key metric in sedative selection. However, traditionally used instruments, e.g., Richmond Agitation-Sedation Scale (Sessler et al., 2002), are subjective and inappropriate for patients prescribed neuromuscular blocking drugs (Hughes et al., 2012). In addition to being appropriate for a broader range of patients and providing subjective assessments, BIS monitors sedation depth continuously. The inclusion of BIS data allows the CDS to learn in real-time about individual patient responses to a given sedative enabling individual-level prediction of the minimum effective dose of given sedative for a specific patient.

CDS outputs:

1) CIBI risk estimates along with confidence intervals from ICU admission time until now (Figure 2);
2) CIBI hazard ratio conditional on sedative options with multiple point estimates extending from now until a user-specified time end-point (Figure 3);
3) Estimate of a minimum effective dose for a given sedation depth level with confidence intervals (Figure 4).

Workflow analysis based on interviews with intensivists and prior literature (Malhotra, Jordan, Shortliffe, & Patel, 2007) suggests that the CDS will play a vital role in multiple tasks including both planning (attending, resident) as well as the delivery of care (attending, resident, nurse; see Table 1).

	attending					nurse			resident		
	patient transfer planning	clinical rounds	consults for patients	procedures related to management	planning for the next day	daily planning	delivery of treatment	cleaning, changing, bed rotations	clinical rounds	consults for patients	post round procedures
CDS sedation	x	informs	informs	informs	informs	x	informs	x	informs	informs	informs

Table 1. Sedation choice CDS and ICU workflow

The main challenge in algorithm development is the lack of immediately accessible labeled data to enable supervised learning. As CIBI assessment in the ICU is rare and often unreliable due to the prevalence of sedation, the development of such an algorithm requires reliance on cognitive assessments conducted after ICU discharge. However, due to the strong predictive power of delirium in CIBI and availability of relevant data, initial efforts could be directed at developing delirium risk assessment algorithm, which 1) is likely to achieve satisfactory performance in predicting CIBI and 2) could later be used as input to the CIBI-oriented algorithm. To evaluate the feasibility of the proposed algorithm, we used MIMIC III, which is a rich dataset which includes time series of multiple health parameters along with information about delirium episodes. Further development of the algorithm could be based on this dataset. BIS data collected using Bispectral Index monitors could be used to develop a model for minimum effective dose estimation.

When applied to sedation selection, computational algorithms for minimum effective sedative dose estimation, as well as CIBI and delirium risk assessment and prediction, have the potential to 1) increase intensivists' efficiency, 2) increase patients' health outcomes, and 3) reduce hospital costs, making such an offering appealing to various stakeholders. As there are no competing products, entering this space can disrupt the ICU health technology market and provide first-mover's advantage.

System architecture

OVERVIEW

The system includes the following elements (Figure 5):

1. Components that produce a set of inputs:
    a. An interface to an EHR to produce medical history and related inputs.
    b. Interfaces to sensors and processing components producing, for example, sedation depth estimation.
    c. Components allowing a clinician to provide additional inputs, such as sedative treatment options under consideration.
2. CIBI risk assessment and risk trajectory prediction module which consumes input data produced by the above components and outputs an estimate of the current risk of CIBI, predicted likelihood of CIBI for clinician-specified pharmacotherapeutic parameters.
3. Minimum effective dose recommendation prediction module, which consumes input data produced by the above components and outputs personalized minimum effective dose estimates for clinician-specified sedation parameters.
4. CIBI risk assessment and risk trajectory prediction visualization module.
5. Minimum effective dose prediction visualization module.

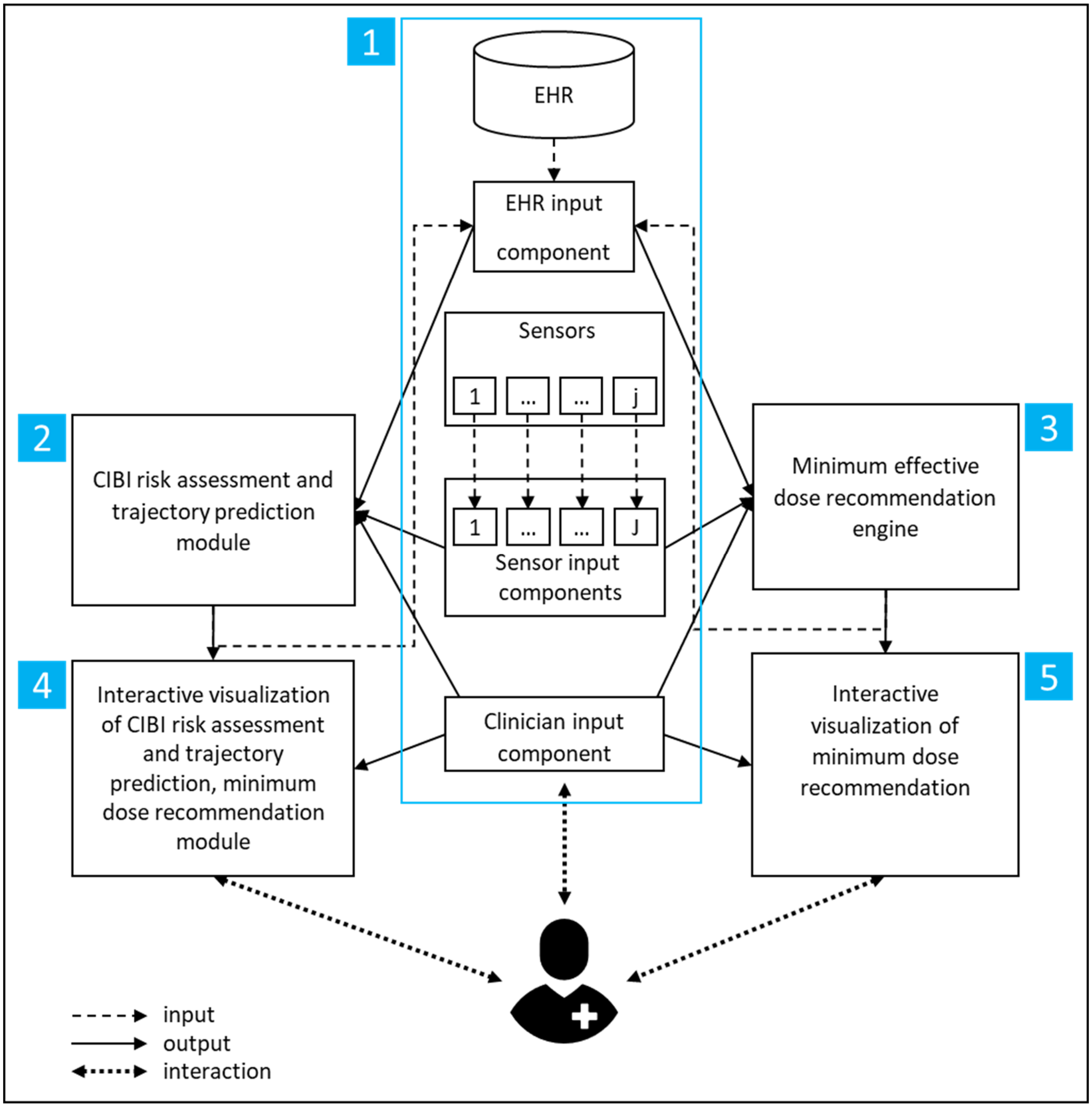

Figure 5. System diagram. See the "Detailed description of the system" section for more details.

DETAILED DESCRIPTION OF THE SYSTEM

Details of specified components follow, with components numbered as above.

1. Components that produce sensor and other inputs may produce a variety of inputs from a variety of sources, varying by embodiment:
    a. Components producing inputs from an EHR:
        i. Medical history: sepsis, preexisting depression, preexisting cognitive impairment, the presence of APOE4, electrolyte imbalances; especially hyponatremia and hypocalcemia, medication history (including steroid use), APACHE IV score,

ii. Disease severity and mortality prediction measures taken at ICU admission, such as the Acute Physiology and Chronic Health Evaluation (APACHE) IV, or the Simplified Acute Physiology Scale (SAPS) II.
iii. Demographic predictors such as age, gender, weight, and height, number of cigarettes per day, number of alcoholic drinks per day.
iv. Current ICU treatment data: sedation (what sedative was used, for how long, time of administration, dose), electrolyte data; especially hyponatremia and hypocalcemia (time, length, severity), hypotension (onset, levels), time spent in delirium (if any; onset, length), steroid use (what steroid was used, for how long, time of administration, dose), cognitive status, liver enzymes, kidney health parameters, cardiovascular health biomarkers.

b. Components producing input from sensors, including:
   i. Sedation depth captured by bispectral index or a broader range of EEG features
   ii. Sleep parameters captured by wearable sensors, a ballistocardiographic sensor or video camera

c. Components allowing input from clinicians:
   i. assessment of airway neurological function, Glasgow Coma score and Confusion Assessment Method score.

2. CIBI risk assessment and risk trajectory prediction module, which applies one or more machine learning algorithms such as: logistic regression, boosting, and regularized variants of these models (e.g., lasso, ridge, and elastic net), trained on previous ICU data, and consumes input data produced by the above components, and outputs an estimate of current risk of CIBI, predicted likelihood of CIBI for clinician-specified treatment parameters (sedative type and dose).
3. Minimum effective dose recommendation prediction engine, which applies one or more machine learning algorithms (e.g. logistic regression, boosting, etc.), regularized variants of these models (e.g. lasso, ridge, and elastic net), and their combinations trained on previous ICU data, and consumes input data produced by the above components, and outputs estimates of the minimum effective dose of a given sedative for a specific patient to reach or maintain a clinician-specified sedation depth.
4. CIBI risk assessment and risk trajectory prediction visualization module, which presents 1) estimated past and current CIBI risk, 2) the likelihood of CIBI given sedative treatment parameters (sedative type and dose) considered by a clinician.
5. Recommended minimum effective dose prediction visualization module, which presents minimum effective doses of a given sedative for a specific patient across sedation depth levels. The visualization accepts inputs from the clinician. The clinician can select a desired sedative and sedation depth. The visualization dynamically interacts with the minimum effective dose recommendation prediction engine and displays the information requested by the clinician, i.e., the minimum effective dose recommendation for entered medication and sedation depth.

Patient-centric system for optimizing sleep efficiency and care scheduling

Insufficient sleep efficiency is detrimental to recovery from a critical illness and was shown to be a risk factor for delirium (Kamdar, Needham, & Collop, 2012; Pulak & Jensen, 2016). Sadly, sleep deprivation in the ICU is particularly common due to pathophysiological (stress, organ dysfunction, inflammatory response, pain, psychosis) and environmental (noise, lighting practices, patient care activities, diagnostic procedures, sedatives, and analgesics) factors (Beltrami et al., 2015; Friese, 2008). One of the interviewed clinicians explained that during night shifts in ICUs it is common to see TVs "blasting," all lights being on, and bed rotation being done. Similar personal accounts are present in the literature (Hinton, 2016). Development of an integrated ICU solution for improving sleep efficiency has the potential to aid recovery as well as decrease the likelihood of suffering from delirium and CIBI.

Background

While modifying pathophysiological factors is likely to be a challenge, the environmental ones could be relatively easily adjusted to improve patients' sleep parameters. One study reported that a very low-tech solution, i.e., ear plugs, vastly reduced patients' confusion (hazard ratio = 0.47, CI = [0.27; 0.82]) showing great promise in preventing delirium, and consequently, CIBI (Arumugam et al., 2017; Van Rompaey, Elseviers, Van Drom, Fromont, & Jorens, 2012). Using a small-scale experiment (n=4), a group of researchers demonstrated that introduction of white noise machines to ICU rooms can restore normal sleep architecture by lowering patients' arousal (Stanchina, Abu-Hijleh, Chaudhry, Carlisle, & Millman, 2005). Beyond sound isolation and masking, behavioral modifications provide another opportunity for reducing ICU noise (Xie, Kang, & Mills, 2009). Among tested interventions were lowering the intensity of night alarms, turning off phones, radios, and TVs (Walder, Francioli, Meyer, Lançon, & Romand, 2000) as well as introducing non-disturbance periods (Monsén & Edéll-Gustafsson, 2005).

Opportunities

Development of a comprehensive technological solution for improving critical illness recovery by increasing sleep efficiency has the potential to prevent delirium and CIBI. As the vast majority of ICU patients are deeply sedated and typically do not interact with any ICU-specific health technologies, this proposal represents a unique opportunity for developing a patient-centric ICU informatics solution to meet their needs. Figure 6 depicts components of the proposed solution interwoven into hospital rooms. Synchronization of lights, window blinds (1) and entertainment systems with the patient's circadian rhythm would help to maintain good sleep hygiene and contribute to lowering confusion. White noise machine (2) and a thick isolation layer (3) would mask and reduce outside noises. A ballistocardiographic sensor integrated into the bed (4) would monitor the patient's sleep quality. By capturing heart rate variability, it would provide additional insight into the patient's recovery. Inferred sleep status could be displayed on room door (5) to reduce awakenings by limiting unnecessary interruptions.

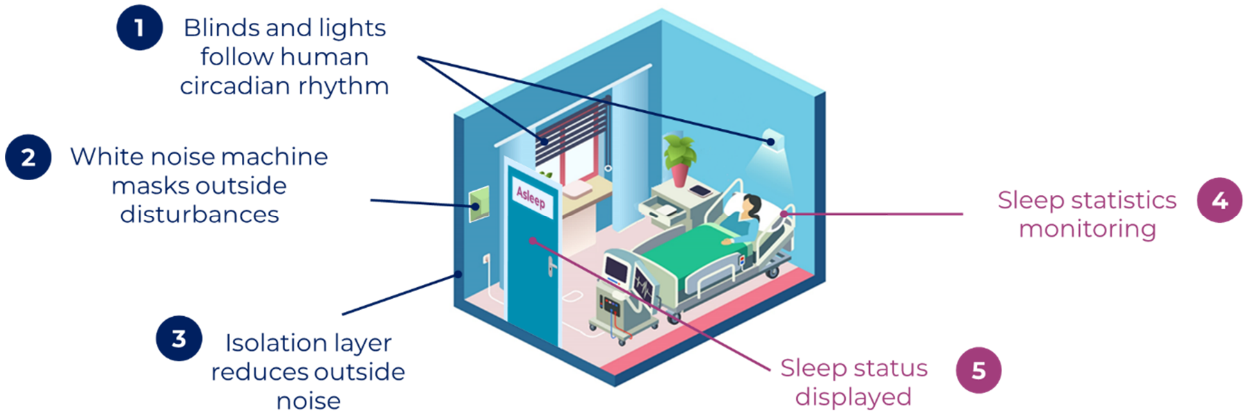

Figure 6. Illustration of proposed technologies to improve sleep efficiency

Sleep data would be easily available at nursing stations (Figure 7). At a glance, care providers would be able to get a high-level overview of sleep parameters. Information about scheduled rest periods would advise caregivers when not to interrupt patients and act as a CDS in care organization. Active, non-rest, periods would guide nursing staff in scheduling and optimizing their care by grouping disruptive activities, e.g., bed rotations and bed-baths, outside of rest time.

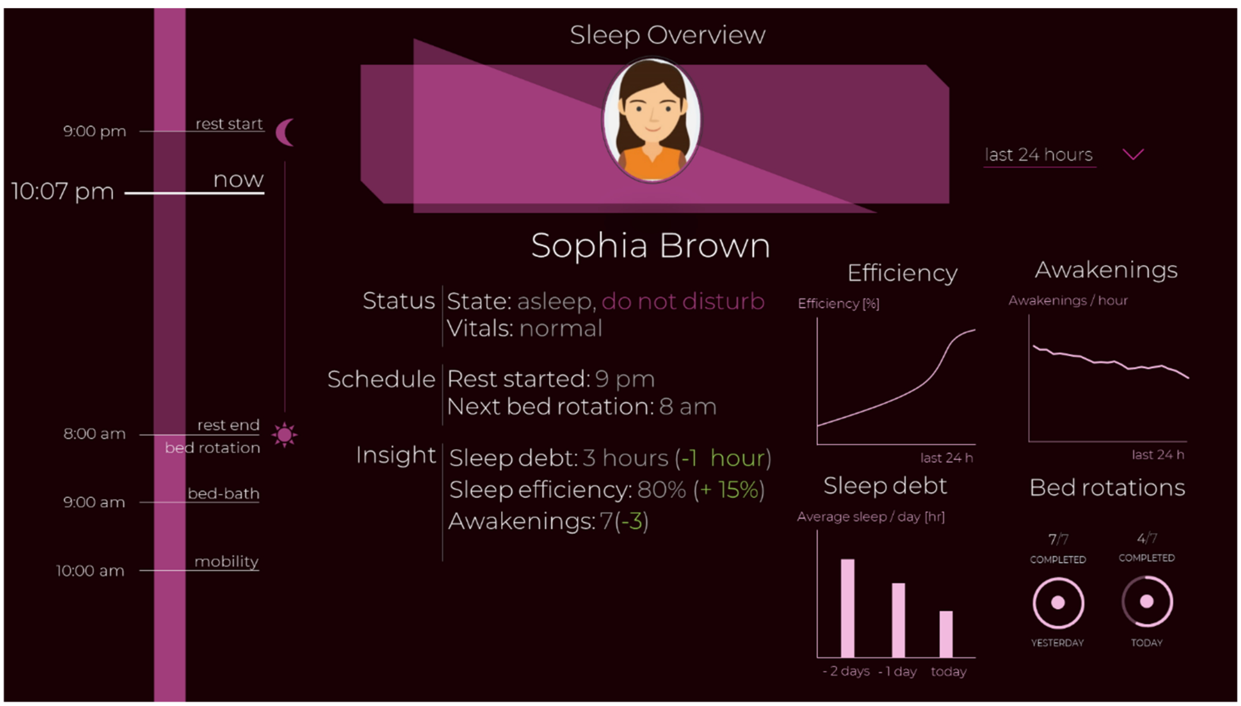

Figure 7. Sleep efficiency and care organization dashboard (illustration)

	attending					nurse			resident		
	patient transfer planning	clinical rounds	consults for patients	procedures related to management	planning for the next day	daily planning	delivery of treatment	cleaning, changing, bed rotations	clinical rounds	consults for patients	post round procedures
CDS care scheduling	x	schedules	schedules	schedules	informs	informs	schedules	schedules	schedules	schedules	schedules
sleep monitoring	informs	informs	informs	x	informs	informs	informs	x	informs	informs	x

Table 2. Care scheduling and sleep efficiency optimization within an ICU workflow (Malhotra et al., 2007)

System architecture

OVERVIEW

The system includes the following elements (Figure 8):

1. One or more components that produce a set of inputs, such as:
    a. An interface to an EHR, producing medical history and related inputs.
    b. Interfaces to sensors and processing components, producing, for example, patient's movement data during sleep.
    c. Components allowing clinicians and nurses to provide additional inputs.
2. Patient state estimation module, which consumes input data produced by the above components, aggregates them, and outputs, for example, sleep efficiency estimates. Optionally, these estimates may be output back to the EHR.
3. Care delivery optimization module, which consumes the patient's state estimates and outputs an optimized care schedule. Optionally, these estimates may be output back to the EHR.
4. Patient's room control system, which adjusts room parameters, for example, lights, based on inputs from the care delivery optimization module.
5. Sleep efficiency and care scheduling visualization module, which presents the patient's sleep parameters, and an optimized care delivery schedule.

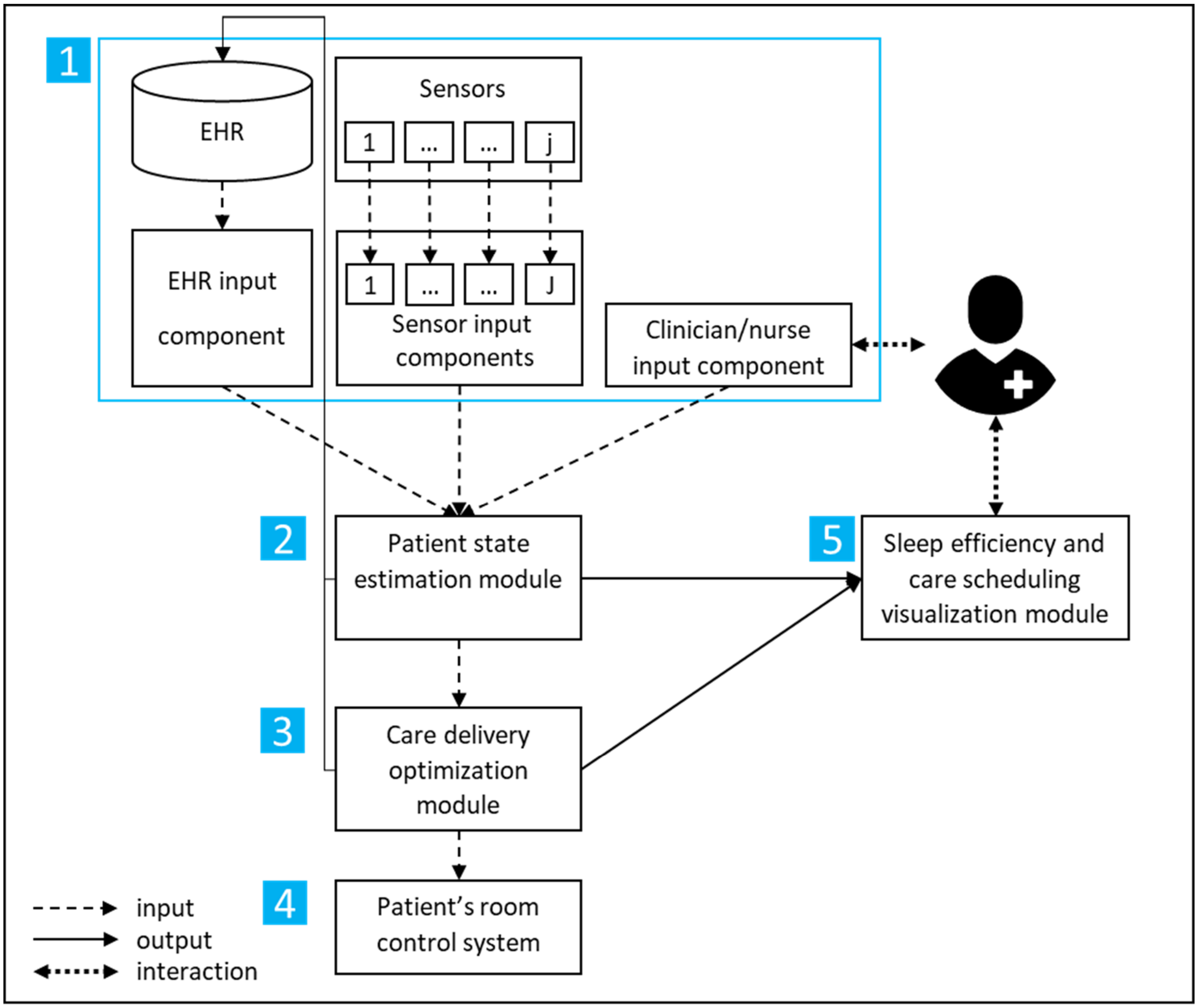

Figure 8. System diagram and data flows.

DETAILED DESCRIPTION OF THE SYSTEM

Details of specified components follow, with components numbered as above.

1. Components that produce sensor and other inputs may produce a variety of inputs from a variety of sources, varying by embodiment:
   a. Components producing inputs from an EHR:
      i. Disease severity and mortality prediction measures taken at ICU admission, such as the Acute Physiology and Chronic Health Evaluation (APACHE) IV, or the Simplified Acute Physiology Scale (SAPS) II.
      ii. Assessments of neurological status at ICU admission, such as National Institutes of Health Stroke Scale (NIHSS) scores.
      iii. Assessment of consciousness impairment at the time of intubation, such as the Glasgow Coma score.
      iv. Complete ICU treatment history, including currently administered sedatives and existing care plan (if available).
      v. Demographic predictors such as age, gender, weight, and height.

    b. Components producing input from sensors, including:
        i. Brain activity captured by bispectral index or a broader range of EEG features
        ii. Sleep parameters captured by wearable sensors, a ballistocardiographic sensor or video camera.
        iii. Oxygen saturation captured by pulse oximetry.
        iv. Electrical activity of the heart data captured by ECG.
        v. Environmental sensors, e.g., light and sound, contact switches installed in door jambs to detect visitors, cameras.
    c. Components allowing input from clinicians and nurses, such as completion of care activities, manual overrides to care delivery schedules, new care activities to be scheduled by the system, and treatment plan changes.
2. Patient state estimation module, which applies one or more machine learning algorithms, and their combinations trained on previous ICU data, and consumes input data produced by the above components, aggregates them, computes intermediate state metrics (heart rate variability, resting heart rate, respiratory rate over a centered, moving 5 minute-window; minimum heart rate, the number of awakenings, sleep depth and stages, total sleep time, sleep debt). The module outputs sleep efficiency and recovery estimates. Optionally, these estimates may be output back to the EHR.
3. Care delivery optimization module, which applies one or more machine learning algorithms, and their combinations trained on previous ICU data, and consumes patient's state estimates and outputs an optimized care schedule, including the timing of bed rotations, bed-baths, mobility exercises, extubation attempts, injections, and visiting hours. Optionally, these estimates may be output back to the EHR.
4. Patient's room control system, which consumes inputs from the care delivery optimization module and adjusts room parameters, i.e., lights, media and sound masking volume, the position of the blinds, and displays patient's sleep status (asleep, resting, awake) on the door.
5. Sleep efficiency and care scheduling visualization module, which consumes inputs from the patient state estimation and the care delivery optimization modules and presents patient's sleep and state parameters as well as an optimized care delivery schedule.

Existing solutions

We found no comparable, integrated solutions on the market.

Multiple vendors offer patient entertainment systems, but those are not synchronized with circadian rhythm. Philips Lighting is a dominant player in providing adaptive lighting to hospitals. Its competitors comprise of relatively small, narrowly specialized companies (e.g., Photon Star Lighting) or startups (e.g., CircaLux). A plethora of companies produces white noise machines. While those manufactures largely do not specifically target healthcare, some of them offer specialized solutions (e.g., Cambridge Sound Management). There are multiple consumer sleep monitoring products. However, the healthcare market is much less saturated with Philips Respironics offering an impressive array of products. Patient monitoring is a common offering among healthcare vendors. Those systems, however, do not provide about sleep efficiency parameters.

In summary, while individual components of the proposed solution exist, no vendor offers them as an integrated ICU bundle. As evidenced by earlier-referenced studies, providing a comprehensive solution for improving sleep efficiency can significantly improve patients' health outcomes.

Clinical decision support for extubation readiness

Sedating intubated patients is a common, and often well-justified, practice (Lapinsky, 2015). In 2009, there were 723,310 mechanically ventilated (MV) patients in the US (Mehta et al., 2015); 85% of MV patients are sedated; 42% of the time they are considered to be under deep sedation (Grap et al., 2012). As outlined earlier, the length of sedation is a strong predictor of delirium and CIBI. Consequently, intensivists need to balance intubation's immediate life-saving effects (e.g., providing sufficient oxygen supply) with its' medium- to long-term threats to patients' health (Divatia, Khan, & Myatra, 2011). The authors of the ABCDEF bundle highlight the importance of extubation by encouraging Spontaneous Breathing Trials (E. W. Ely, 2017). However, failed extubation may lead to adverse effects. Correlation studies suggest that extubation failure incurs higher costs, extends the length of morbidity and stay in the ICU and the hospital as well as increases mortality (Kulkarni & Agarwal, 2008). With an average failure rate of 15%, the decision to extubate is, therefore, not inconsequential (Thille & Boissier, 2016). While there exist extubation readiness protocols, they are not yet widely implemented. Furthermore, those protocols rely on a relatively small subset of predictors and are not tailored to individual patients.

We propose developing a comprehensive clinical decision support system to aid in assessing extubation readiness. The proposed CDS would rely on a computational, evidence-based algorithm providing individual-level extubate success predictions based on medical history and real-time ICU data (Figure 9). Furthermore, the system would warn against extubations if the probability of extubation success was below a predefined threshold.

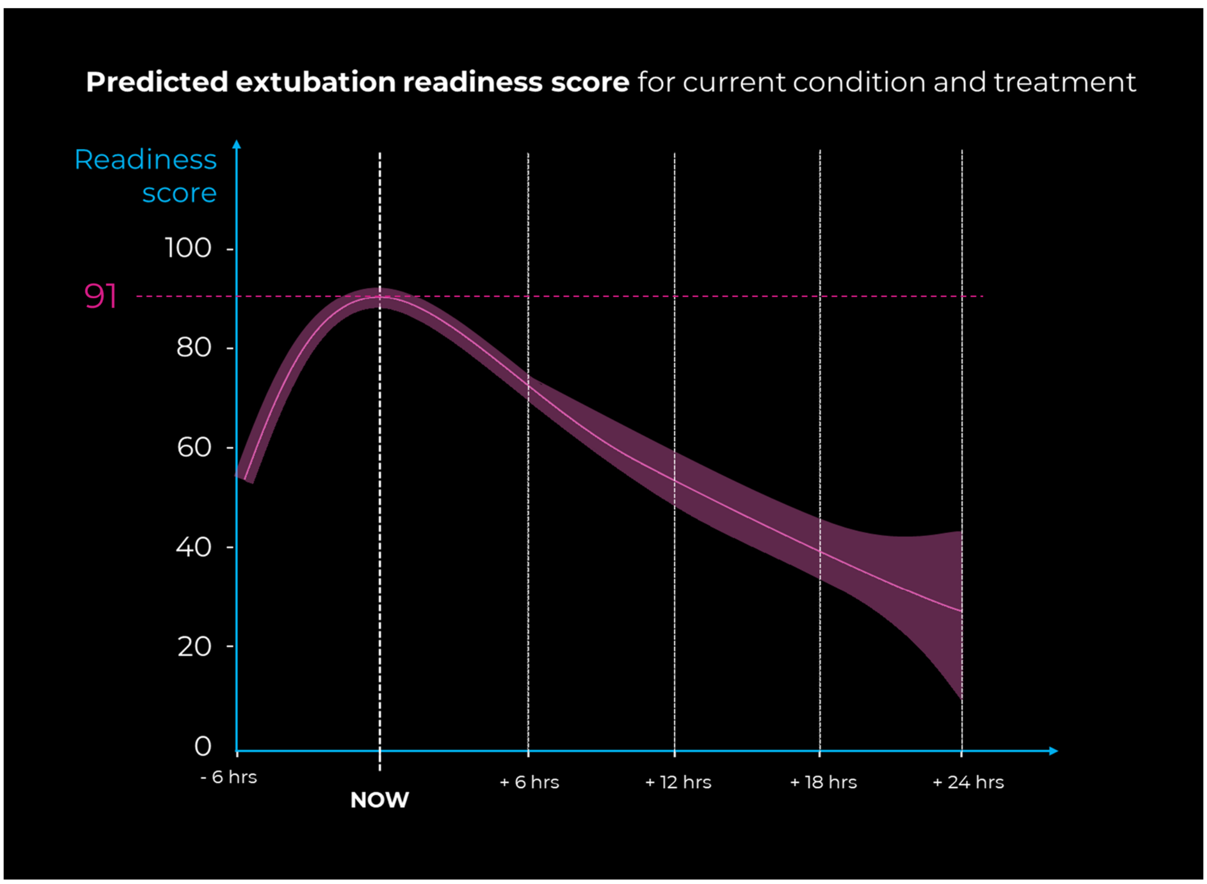

Figure 9. Extubation readiness prediction (illustration)

Background

The term “extubation failure” refers to the inability to continue breathing spontaneously and requiring reintubation within a given time interval (24 hours to 7 days) after ceasing mechanical ventilation and removing tracheostomy or endotracheal tube (Kulkarni & Agarwal, 2008). Failed extubations are associated with high mortality (25-50%) (Thille & Boissier, 2016), increased likelihood of dying in the hospital (43% vs. 12%), longer stay in the ICU and in the hospital, and more likely need for treatment in a rehabilitation or long-term care facility (Epstein, Ciubotaru, & Wong, 1997). In their extubation decisions, intensivists need to balance extubation benefits (e.g., shorter length of sedation, lower cost of care) and risks.

Recent research suggests that the complexity of this decision leads to suboptimal outcomes. When compared to protocols predicting successful extubations, extubations directed by physicians were associated with a higher reintubation rate and increased length of hospital stay (Guijo González et al., 2015). Implementation of formalized extubation readiness protocols leads to a shorter duration of mechanical ventilation (Asehnoune et al., 2017; Roquilly et al., 2013), more ICU-free days (Asehnoune et al., 2017; Guijo González et al., 2015; Roquilly et al., 2013), fewer reintubations (Guijo González et al., 2015), and lower mortality (Asehnoune et al., 2017).

Multiple studies tried to identify predictors of failed extubations (Thille, Richard, & Brochard, 2013). Based on this research, candidate inputs into the CDS include:

1. Medical history: high Acute Physiology And Chronic Health Evaluation (APACHE) II (Knaus, Draper, Wagner, & Zimmerman, 1985), Simplified Acute Physiology Scale (SAPS) II (Gall, Lemeshow, & Saulnier, 1993), National Institutes of Health Stroke Scale (NIHSS) (Kwah & Diong, 2014) scores at ICU admission, preoperative comorbidities, extended ventilation duration and cardiopulmonary bypass, multiple transfusions (>10 units), displacement of liver/spleen, thoracic aorta surgeries, pneumonia (Frutos-Vivar et al., 2006; Kulkarni & Agarwal, 2008; Lee, Hui, Chan, Tan, & Lim, 1994; Lioutas, Hanafy, & Kumar, 2016; Meade et al., 2001)
2. Respiratory parameters: rapid shallow breathing index, airway occlusion pressure at 1s, the ratio of occlusion pressure to maximum inspiratory pressure, minute ventilation recovery time, work of breathing (Kulkarni & Agarwal, 2008 and references therein)
3. Airway competence: cough strength, endotracheal secretions, neurological function (Kulkarni & Agarwal, 2008 and references therein)
4. Other: dysarthria (Lioutas et al., 2016); the Glasgow Coma Scale (Sternbach, 2000) at intubation (Guru, Singh, Pedavally, Rabinstein, & Hocker, 2016) and extubation time (Asehnoune et al., 2017), age (Kulkarni & Agarwal, 2008 and references therein)

The relevance of the above predictors is cohort specific. For instance, while some studies identified respiratory parameters to be predictive of extubation success (Capdevila, Perrigault, Perey, Roustan, & d’Athis, 1995), other did not find such a relationship (Lioutas et al., 2016). These seemingly conflicting results may originate from different etiology of the original critical illnesses as well as dissimilar treatment or weaning protocols. Furthermore, predictors validated on adults do not reliably predict extubation success in children and infants (Venkataraman, Khan, & Brown, 2000). A robust algorithm for predicting extubation success needs to account for such differences. Nascent research in this space (Tu, Chang, Chang, Lee, & Chang, 2018) demonstrates the validity of such an approach.

We propose that outputs of the system include estimation of extubation readiness including confidence intervals (assuming stable condition and maintenance of current treatment) and warnings when extubation readiness score is below a predefined threshold.

Existing solutions

To the best of our knowledge, there exist no CDS that predicts extubation success.

Dräger offers an automated weaning protocol to reduce ventilation time called SmartCare®/ PS[3]. The efficacy of this protocol was demonstrated in a peer-reviewed study (Burns, Lellouche, Nisenbaum, Lessard, & Friedrich, 2014). It is conceivable that the development of an algorithm to predict extubation success is underway.

Opportunities

One weakness of Dräger's solution is reliance solely on respiratory parameters. Development of a computational CDS integrating both respiratory parameters and other inputs listed in the Background section would help establish a strong position in this space and support sales of relevant ICU products.

This CDS is to support three main ICU actors, i.e., attending, nurses, and residents, in patient care across multiple tasks (Table 3). In addition to providing information during all relevant activities, the system also warns against extubation if patients' relevant vitals rapidly decline (Malhotra et al., 2007).

	attending					**nurse**			**resident**		
	patient transfer planning	clinical rounds	consults for patients	procedures related to management	planning for the next day	daily planning	delivery of treatment	cleaning, changing, bed rotations	clinical rounds	consults for patients	post round procedures
CDS extubation	informs	informs	informs	informs warns	informs	informs	informs warns	x	informs	informs	informs warns

Table 3. Extubation success CDS and ICU workflow

By helping intensivists decide when to extubate, this solution:

1) improves patients' health outcomes by lowering CIBI and delirium risk due to prolonged mechanical ventilation and time under sedation, and reducing the likelihood of failed extubations
2) reduces care costs by shortening ICU stay, lowering, and decreasing ICU care providers' workload

System architecture

OVERVIEW

The system includes the following elements (Figure 10):

6. One or more components that produce a set of inputs, such as:
    a. An interface to an EHR, producing medical history and related inputs.

[3] https://www.draeger.com/en_uk/Hospital/Products/Ventilation-and-Respiratory-Monitoring/ICU-Ventilation-and-Respiratory-Monitoring/SmartCare-PS-The-automated-weaning-protocol

   b. Interfaces to sensors and processing components, producing, for example, a variety of respiratory parameters.
   c. Components allowing a clinician to provide additional inputs.
7. An extubation success prediction module, which consumes input data produced by the above components and outputs a predicted likelihood of successful extubation (defined as lack of re-intubation, death, or other specified adverse outcomes within a specified time period after extubation). Optionally, this prediction may be output back to the EHR or other long-term storage.
8. An extubation risk/readiness visualization module, which presents a score summarizing extubation risk and readiness to a clinician.

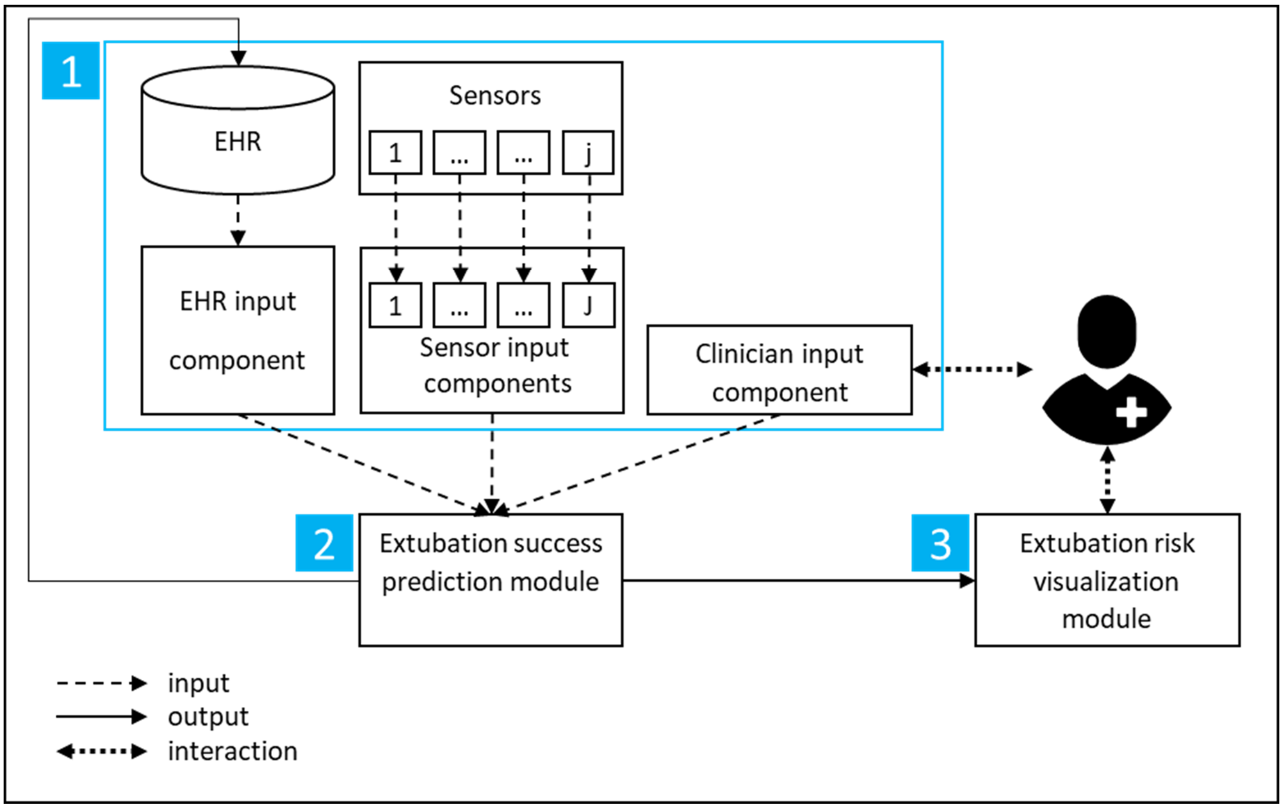

Figure 10. System diagram and data flows.

DETAILED DESCRIPTION OF THE SYSTEM

Details of specified components follow, with components numbered as above.

6. Components that produce sensor and other inputs may produce a variety of inputs from a variety of sources, varying by embodiment:
   a. Components producing inputs from an EHR:
      i. Disease severity and mortality prediction measures taken at ICU admission, such as the Acute Physiology and Chronic Health Evaluation (APACHE) IV, or the Simplified Acute Physiology Scale (SAPS) II.
      ii. Assessments of neurological status at ICU admission, such as National Institutes of Health Stroke Scale (NIHSS) scores.

iii. Assessment of consciousness impairment at time of intubation, such as the Glasgow Coma score.
iv. Potential covariates, such as the presence or absence of preoperative comorbidities, extended ventilation duration and cardiopulmonary bypass, multiple prior transfusions, displacement of liver/spleen, thoracic aorta surgeries, pneumonia, and diagnosed COPD.
v. Demographic predictors such as age, gender, weight, and height.
vi. In some embodiments, recorded details and outcomes of prior extubation attempts, either for the same patient or similar patients (as identified by a case matching procedure). Embodiments that use details of prior extubation attempts for the same patient may also include capabilities for storing the output of prior extubation success predictions in the EHR, to be included in those details.

b. Components producing input from sensors, including:
   i. Respiratory parameters and airway competence captured by ventilators, including rapid shallow breathing index, airway occlusion pressure, the ratio of occlusion pressure to maximum inspiratory pressure, minute ventilation recovery time, work of breathing, peak inspiratory flow, peak inspiratory pressure, mean airway pressure, % patient triggered breaths, and I:E ratio.
   ii. Airway competence, including cough peak flow (captured by ventilators or spirometers) endotracheal secretions (captured using airway clearance devices).
   iii. Sedation depth captured by bispectral index.
   iv. Oxygen saturation captured by pulse oximetry.

c. Components allowing input from clinicians, such as assessment of airway neurological function, Glasgow Coma score at extubation, and Confusion Assessment Method scores.

7. The extubation success prediction component may apply a variety of machine learning and/or statistical models, such as: logistic and probit models, regularized variants of these models (e.g. lasso, ridge, and elastic net), auto-encoding networks, generalized discriminant analysis, Bayesian and/or multilinear principal component analysis, classification and regression trees, and their combinations. In some embodiments, this module may be implemented in a discrete component, or remotely (“cloud”). In some embodiments, a specialized/tailored machine learning model and/or algorithm may be chosen case-by-case, e.g. by ward. In some embodiments, the output of this model (e.g., risk score) may be recorded in the EHR, for retrospective review and clinician and/or CDS improvement, or as an additional input signal for other systems (e.g., discharge readiness).
8. In some embodiments, this system may be component of a larger clinical decision support system, displayed alongside other indicators. In some embodiments, the visualization component may proactively indicate (e.g., via a visualization indicator) when extubation should or should not be performed (e.g., when risk is above a specified threshold), while in others, clinicians may request visualization for decision support interactively.

Summary of proposed preventive solutions

The proposed solutions to reduce CIBI risk focus on the most impactful of modifiable risk factors, i.e., on poor sleep efficiency and prolonged, deep sedation. We envision those technologies as embedded into a larger, interactive “ICU of the Future” system. Figure 11 depicts dependencies and data flows between

CIBI-oriented components. Based on our analysis, the system will support attending clinicians, nurses, and residents across multiple in their workflows (Table 4).

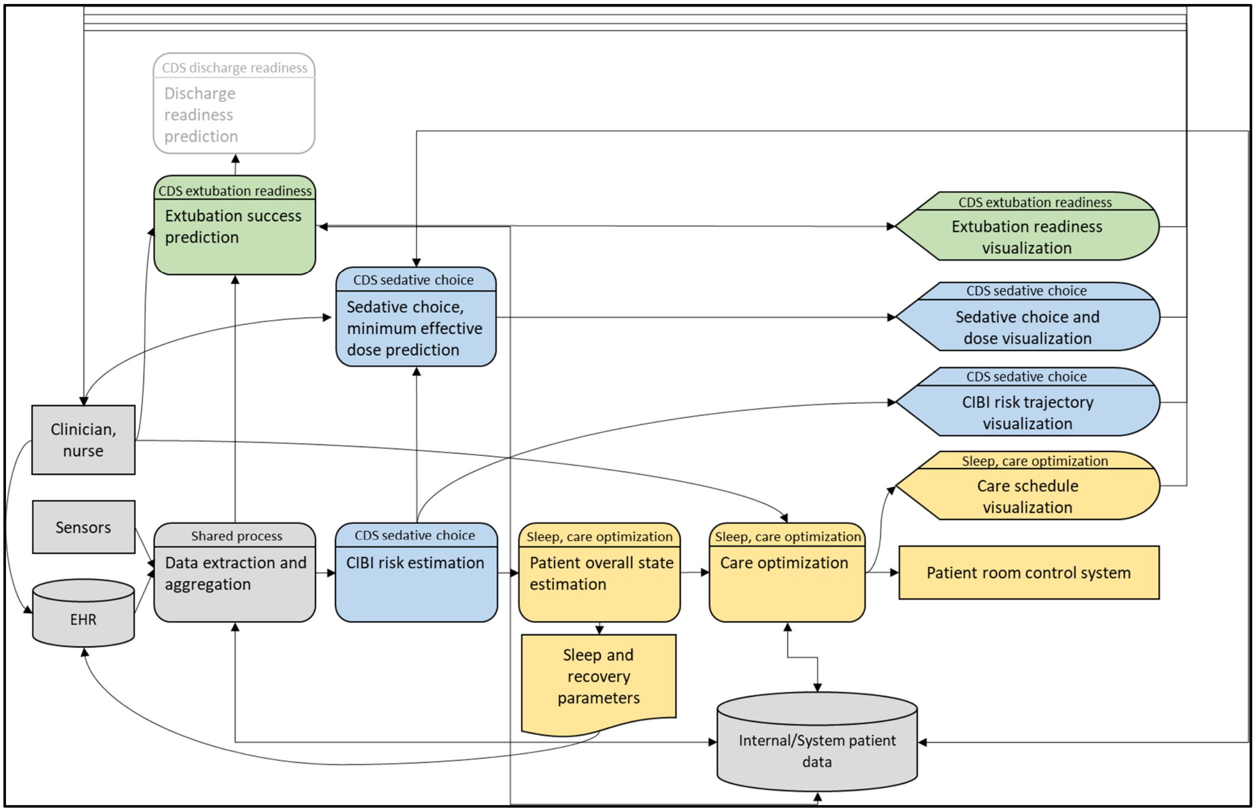

Figure 11. Systems integration: high-level data flow diagram

Relevant sensor and EHR data are extracted and aggregated by a processing component shared across all three proposed systems (Figure 11; in grey). These data are next consumed by: 1) extubation readiness prediction system (in green), which outputs extubation success prediction to a CDS for discharge readiness (not described in this document; greyed out) and displays them as a visualization, 2) the CIBI risk assessment algorithm (in blue) which outputs CIBI risk estimates. Those estimates, along with other data outlined in previous sections, serve as inputs to: 1) sedative choice and minimum effective dose prediction system (in blue), which outputs predictions as a visualization, 2) sleep and care optimization system (in yellow), which estimates patient' sleep and recovery parameters. In addition to exporting those parameters into EHR, the system optimizes care delivery schedule, which is visualized for clinicians and nurses. Furthermore, the system controls patient's room to optimize care environment. All visualizations include interactive components allowing critical care staff to interact with them. Those interactions are captured and processed by respective systems as well as by the EHR. All systems store data in an internal data repository, which implements and enforces pre-specified data access policies, and have access to data generated by other systems.

	attending					nurse			resident		
	patient transfer planning	clinical rounds	consults for patients	procedures related to management	planning for the next day	daily planning	delivery of treatment	cleaning, changing, bed rotations	clinical rounds	consults for patients	post round procedures
CDS sedation	x	informs	informs	informs	informs	x	informs	x	informs	informs	informs
CDS extubation	informs	informs	informs	informs warns	informs	informs	informs warns	x	informs	informs	informs warns
CDS care scheduling	x	schedules	schedules	schedules	informs	informs	schedules	schedules	schedules	schedules	schedules
sleep monitoring	informs	informs	informs	x	informs	informs	informs	x	informs	informs	x

Table 4. Proposed technologies and ICU workflow

Potential impact

With 4,600,000 ICU stays and total charges of $281,800 million (Barrett, Smith, Elixhauser, Honigman, & Pines, 2014), the proposed health informatics technologies have enormous financial impact potential. Their implementation can generate savings for hospitals by lowering re-admission rates, lowering bounce-backs, shortening the length of ICU stays, making care more time- and cost-effective, and reducing legal liability.

These technologies can dramatically improve patients' health. We estimate that in 2009 there were at least 2,346,000 instances of CIBI at discharge, 1,462,800 instances of delirium, 245,925 oversedated mechanically ventilated patients, and 180,750 failed extubations. Development of the proposed technologies can help millions of patients every year by reducing exposure to cognitively toxic sedatives, reducing oversedation, sedation length, risk of delirium and CIBI, length of mechanical ventilation, risk of failed extubation, leading to faster recovery by improved sleep efficiency, shortened hospital stays, and improved HRQOL.

Introduction of those technologies to the market will help hospitals and insurers lower costs of care and help improve patients' lives.

References:

Alosco, M. L., Spitznagel, M. B., van Dulmen, M., Raz, N., Cohen, R., Sweet, L. H., … Gunstad, J. (2012). Cognitive function and treatment adherence in older adults with heart failure. *Psychosomatic Medicine*, *74*(9), 965–973. https://doi.org/10.1097/PSY.0b013e318272ef2a

Ambrosino, N., Bruletti, G., Scala, V., Porta, R., & Vitacca, M. (2002). Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: a controlled study. *Intensive Care Medicine*, *28*(2), 170–177. https://doi.org/10.1007/s00134-001-1165-6

Anderson, R. E., & Birge, S. J. (2016). Cognitive Dysfunction, Medication Management, and the Risk of Readmission in Hospital Inpatients. *Journal of the American Geriatrics Society*, *64*(7), 1464–1468. https://doi.org/10.1111/jgs.14200

Arroliga, A., Frutos-Vivar, F., Hall, J., Esteban, A., Apezteguía, C., Anzueto, A., & Soto, L. (2005). Use of Sedatives and Neuromuscular Blockers in a Cohort of Patients Receiving Mechanical Ventilation. *Chest*, *128*(2), 496–506. https://doi.org/10.1378/CHEST.128.2.496

Arumugam, S., El-Menyar, A., Al-Hassani, A., Strandvik, G., Asim, M., Mekkodithal, A., … Al-Thani, H. (2017). Delirium in the Intensive Care Unit. *Journal of Emergencies, Trauma, and Shock*, *10*(1), 37–46. https://doi.org/10.4103/0974-2700.199520

Asehnoune, K., Seguin, P., Lasocki, S., Roquilly, A., Delater, A., Gros, A., … Blanloeil, Y. (2017). Extubation Success Prediction in a Multicentric Cohort of Patients with Severe Brain Injury. *Anesthesiology*, *127*(2), 338–346. https://doi.org/10.1097/ALN.0000000000001725

Barrett, M. L., Smith, M. W., Elixhauser, A., Honigman, L. S., & Pines, J. M. (2014). Utilization of Intensive Care Services, 2011: Statistical Brief #185. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*.

Beltrami, F. G., Nguyen, X.-L., Pichereau, C., Maury, E., Fleury, B., & Fagondes, S. (2015). Sleep in the intensive care unit. *Jornal Brasileiro de Pneumologia : Publicacao Oficial Da Sociedade Brasileira de Pneumologia e Tisilogia*, *41*(6), 539–546. https://doi.org/10.1590/S1806-37562015000000056

Bergeron, N., Dubois, M.-J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Medicine*, *27*(5), 859–864.

Burns, K. E. A., Lellouche, F., Nisenbaum, R., Lessard, M. R., & Friedrich, J. O. (2014). Automated weaning and SBT systems versus non-automated weaning strategies for weaning time in invasively ventilated critically ill adults. *The Cochrane Database of Systematic Reviews*, (9), CD008638. https://doi.org/10.1002/14651858.CD008638.pub2

Cameron, J., Worrall-Carter, L., Page, K., Riegel, B., Lo, S. K., & Stewart, S. (2010). Does cognitive impairment predict poor self-care in patients with heart failure? *European Journal of Heart Failure*, *12*(5), 508–515. https://doi.org/10.1093/eurjhf/hfq042

Capdevila, X. J., Perrigault, P. F., Perey, P. J., Roustan, J. P., & d'Athis, F. (1995). Occlusion pressure and its ratio to maximum inspiratory pressure are useful predictors for successful extubation following T-piece weaning trial. *Chest*, *108*(2), 482–489. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7634888

Carlson, C., & Huang, D. T. (2013). The Adult Respiratory Distress Syndrome Cognitive Outcomes Study: long-term neuropsychological function in survivors of acute lung injury. *Critical Care*, *17*(3), 317. https://doi.org/10.1186/cc12709

Chanques, G., & Jaber, S. (2007). Sedation assessment tool, sedation-algorithm, choice of sedation drugs: intricate concepts of an emergent clinical practice. *Intensive Care Medicine*, *33*(3), 554–555. https://doi.org/10.1007/s00134-006-0510-1

Cheung, A. M., Tansey, C. M., Tomlinson, G., Diaz-Granados, N., Matté, A., Barr, A., … Group, for the C. C. C. T. (2006). Two-Year Outcomes, Health Care Use, and Costs of Survivors of Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine*, *174*(5), 538–544. https://doi.org/10.1164/rccm.200505-693OC

Clancy, O., Edginton, T., Casarin, A., & Vizcaychipi, M. P. (2015). The psychological and neurocognitive consequences of critical illness. A pragmatic review of current evidence. *Journal of the Intensive Care Society*, *16*(3), 226–233. https://doi.org/10.1177/1751143715569637

de Azevedo, J. R. A., Montenegro, W. S., Rodrigues, D. P., de C Souza, S. C., Araujo, V. F. S., de Paula, M. P., … Mendonça, A. V. N. (2017). Long-term cognitive outcomes among unselected ventilated and non-ventilated ICU patients. *Journal of Intensive Care*, *5*, 18. https://doi.org/10.1186/s40560-017-

0213-4

Desai, S. V., Law, T. J., & Needham, D. M. (2011). Long-term complications of critical care. *Critical Care Medicine*, *39*(2), 371–379. https://doi.org/10.1097/CCM.0b013e3181fd66e5

Divatia, J. V, Khan, P. U., & Myatra, S. N. (2011). Tracheal intubation in the ICU: Life saving or life threatening? *Indian Journal of Anaesthesia*, *55*(5), 470–475. https://doi.org/10.4103/0019-5049.89872

Douglas, V. C., Hessler, C. S., Dhaliwal, G., Betjemann, J. P., Fukuda, K. A., Alameddine, L. R., … Josephson, S. A. (2013). The AWOL tool: Derivation and validation of a delirium prediction rule. *Journal of Hospital Medicine*, *8*(9), 493–499. https://doi.org/10.1002/jhm.2062

Egerod, I., Christensen, B. V., & Johansen, L. (2006). Trends in sedation practices in Danish intensive care units in 2003: a national survey. *Intensive Care Medicine*, *32*(1), 60–66. https://doi.org/10.1007/s00134-005-2856-1

Eide, L. S. P., Ranhoff, A. H., Fridlund, B., Haaverstad, R., Hufthammer, K. O., Kuiper, K. K. J., … CARDELIR Investigators. (2016). Readmissions and mortality in delirious versus non-delirious octogenarian patients after aortic valve therapy: a prospective cohort study. *BMJ Open*, *6*(10), e012683. https://doi.org/10.1136/bmjopen-2016-012683

Elizabeth Wilcox, M., Brummel, N. E., Archer, K., Wesley Ely, E., Jackson, J. C., & Hopkins, R. O. (2013). Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Critical Care Medicine*, *41*(9 SUPPL.1), 81–98. https://doi.org/10.1097/CCM.0b013e3182a16946

Elliott, R., McKinley, S., Aitken, L. M., & Hendrikz, J. (2006). The effect of an algorithm-based sedation guideline on the duration of mechanical ventilation in an Australian intensive care unit. *Intensive Care Medicine*, *32*(10), 1506–1514. https://doi.org/10.1007/s00134-006-0309-0

Elsamadicy, A. A., Wang, T. Y., Back, A. G., Lydon, E., Reddy, G. B., Karikari, I. O., & Gottfried, O. N. (2017). Post-operative delirium is an independent predictor of 30-day hospital readmission after spine surgery in the elderly (≥65 years old): A study of 453 consecutive elderly spine surgery patients. *Journal of Clinical Neuroscience*, *41*, 128–131. https://doi.org/10.1016/j.jocn.2017.02.040

Ely, E. W. (2017). The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. *Critical Care Medicine*, *45*(2), 321–330. https://doi.org/10.1097/CCM.0000000000002175

Ely, E. W., Baker, A. M., Evans, G. W., & Haponik, E. F. (2000). The distribution of costs of care in mechanically ventilated patients with chronic obstructive pulmonary disease. *Critical Care Medicine*, *28*(2), 408–413.

Ely, W. E., Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Thomason, J. W. W., … Laskowitz, D. T. (2007). Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients*. *Critical Care Medicine*, *35*(1), 112–117. https://doi.org/10.1097/01.CCM.0000251925.18961.CA

Epstein, S. K., Ciubotaru, R. L., & Wong, J. B. (1997). Effect of Failed Extubation on the Outcome of Mechanical Ventilation. *Chest*, *112*(1), 186–192. https://doi.org/https://doi.org/10.1378/chest.112.1.186

Friese, R. S. (2008). Sleep and recovery from critical illness and injury: A review of theory, current practice, and future directions*. *Critical Care Medicine*, *36*(3), 697–705.

https://doi.org/10.1097/CCM.0B013E3181643F29

Frutos-Vivar, F., Ferguson, N. D., Esteban, A., Epstein, S. K., Arabi, Y., Apezteguía, C., … Anzueto, A. (2006). Risk Factors for Extubation Failure in Patients Following a Successful Spontaneous Breathing Trial. *Chest*, *130*(6), 1664–1671. https://doi.org/10.1378/chest.130.6.1664

Gall, J. R., Lemeshow, S., & Saulnier, F. (1993). A New Simplified Acute Physiology Score (SAPS II) Based on a European/North American Multicenter Study. *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.1993.03510240069035

Girard, T. D., Dittus, R. S., & Ely, E. W. (2016). Critical Illness Brain Injury. *Annual Review of Medicine*, *67*(1), 497–513. https://doi.org/10.1146/annurev-med-050913-015722

Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Pun, B. T., Henderson, M. S., … Ely, E. W. (2007). Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. *Critical Care*, *11*(1), R28. https://doi.org/10.1186/cc5708

Gordon, S. M., Jackson, J. C., Ely, E. W., Burger, C., & Hopkins, R. O. (2004). Clinical identification of cognitive impairment in ICU survivors: Insights for intensivists. *Intensive Care Medicine*, *30*(11), 1997–2008. https://doi.org/10.1007/s00134-004-2418-y

Grap, M. J., Munro, C. L., Wetzel, P. A., Best, A. M., Ketchum, J. M., Hamilton, V. A., … Sessler, C. N. (2012). Sedation in adults receiving mechanical ventilation: physiological and comfort outcomes. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses*, *21*(3), e53–63; quiz e64. https://doi.org/10.4037/ajcc2012301

Guijo González, P., Estella, Á., Ramos Rodríguez, J., Rico Armenteros, T., Jaen Franco, M., Recuerda, M., … Fernández Ruiz, L. (2015). Implementation of a protocol for predicting successful extubation in critically ill patients. *Intensive Care Medicine Experimental*, *3*(Suppl 1), A316. https://doi.org/10.1186/2197-425X-3-S1-A316

Guillamondegui, O. D., Richards, J. E., Ely, E. W., Jackson, J. C., Archer-Swygert, K., Norris, P. R., … Obremskey, W. T. (2011). Does Hypoxia Affect Intensive Care Unit Delirium or Long-Term Cognitive Impairment After Multiple Trauma Without Intracranial Hemorrhage? *The Journal of Trauma: Injury, Infection, and Critical Care*, *70*(4), 910–915. https://doi.org/10.1097/TA.0b013e3182114f18

Guru, P. K., Singh, T. D., Pedavally, S., Rabinstein, A. A., & Hocker, S. (2016). Predictors of Extubation Success in Patients with Posterior Fossa Strokes. *Neurocritical Care*, *25*(1), 117–127. https://doi.org/10.1007/s12028-016-0249-7

Halpern, N. A., & Pastores, S. M. (2015). Critical Care Medicine Beds, Use, Occupancy, and Costs in the United States. *Critical Care Medicine*, *43*(11), 2452–2459. https://doi.org/10.1097/CCM.0000000000001227

Hinton, L. (2016). The intensive care unit was so noisy I couldn't sleep. *BMJ (Clinical Research Ed.)*, *353*, i2150. https://doi.org/10.1136/BMJ.I2150

Hopkins, R. O., & Brett, S. (2005). Chronic neurocognitive effects of critical illness. *Current Opinion in Critical Care*, *11*(4), 369–375. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16015118

Hopkins, R. O., & Jackson, J. C. (2006). Long-term Neurocognitive Function After Critical Illness. *Chest*, *130*(3), 869–878. https://doi.org/10.1378/CHEST.130.3.869

Hopkins, R. O., Suchyta, M. R., Snow, G. L., Jephson, A., Weaver, L. K., & Orme, J. F. (2010). Blood glucose dysregulation and cognitive outcome in ARDS survivors. *Brain Injury*, *24*(12), 1478–1484. https://doi.org/10.3109/02699052.2010.506861

Hopkins, R. O., Weaver, L. K., Chan, K. J., & Orme, J. F. (2004). Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *Journal of the International Neuropsychological Society : JINS*, *10*(7), 1005–1017. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15803563

Hopkins, R. O., Weaver, L. K., Collingridge, D., Parkinson, R. B., Chan, K. J., & Orme, J. F. (2005). Two-Year Cognitive, Emotional, and Quality-of-Life Outcomes in Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine*, *171*(4), 340–347. https://doi.org/10.1164/rccm.200406-763OC

HOPKINS, R. O., WEAVER, L. K., POPE, D., ORME, J. F., BIGLER, E. D., & LARSON-LOHR, V. (1999). Neuropsychological Sequelae and Impaired Health Status in Survivors of Severe Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine*, *160*(1), 50–56. https://doi.org/10.1164/ajrccm.160.1.9708059

Hsieh, S. J., Ely, E. W., & Gong, M. N. (2013). Can intensive care unit delirium be prevented and reduced? Lessons learned and future directions. *Annals of the American Thoracic Society*, *10*(6), 648–656. https://doi.org/10.1513/AnnalsATS.201307-232FR

Hsu, Y.-H., Lin, F.-S., Yang, C.-C., Lin, C.-P., Hua, M.-S., & Sun, W.-Z. (2015). Evident cognitive impairments in seemingly recovered patients after midazolam-based light sedation during diagnostic endoscopy. *Journal of the Formosan Medical Association*, *114*(6), 489–497. https://doi.org/10.1016/J.JFMA.2013.07.018

Hughes, C. G., McGrane, S., & Pandharipande, P. P. (2012). Sedation in the intensive care setting. *Clinical Pharmacology : Advances and Applications*, *4*, 53–63. https://doi.org/10.2147/CPAA.S26582

Inouye, S. K., Bogardus, S. T., Charpentier, P. A., Leo-Summers, L., Acampora, D., Holford, T. R., & Cooney, L. M. (1999). A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. *New England Journal of Medicine*, *340*(9), 669–676. https://doi.org/10.1056/NEJM199903043400901

Iwashyna, T. J., Ely, E. W., Smith, D. M., & Langa, K. M. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*, *304*(16), 1787–1794. https://doi.org/10.1001/jama.2010.1553

Jackson, D. L., Proudfoot, C. W., Cann, K. F., & Walsh, T. S. (2009). The incidence of sub-optimal sedation in the ICU: a systematic review. *Critical Care (London, England)*, *13*(6), R204. https://doi.org/10.1186/cc8212

Jackson, J. C., Archer, K. R., Bauer, R., Abraham, C. M., Song, Y., Greevey, R., … Obremskey, W. (2011). A Prospective Investigation of Long-Term Cognitive Impairment and Psychological Distress in Moderately Versus Severely Injured Trauma Intensive Care Unit Survivors Without Intracranial Hemorrhage. *The Journal of Trauma: Injury, Infection, and Critical Care*, *71*(4), 860–866. https://doi.org/10.1097/TA.0b013e3182151961

Jackson, J. C., Girard, T. D., Gordon, S. M., Thompson, J. L., Shintani, A. K., Thomason, J. W. W., … Ely, E. W. (2010). Long-term Cognitive and Psychological Outcomes in the Awakening and Breathing

Controlled Trial. *American Journal of Respiratory and Critical Care Medicine*, *182*(2), 183–191. https://doi.org/10.1164/rccm.200903-0442OC

Jackson, J. C., Hart, R. P., Gordon, S. M., Shintani, A., Truman, B., May, L., & Ely, E. W. (2003). Six-month neuropsychological outcome of medical intensive care unit patients. *Critical Care Medicine*, *31*(4), 1226–1234. https://doi.org/10.1097/01.CCM.0000059996.30263.94

Jackson, J. C., Obremskey, W., Bauer, R., Greevy, R., Cotton, B. A., Anderson, V., … Ely, E. W. (2007). Long-Term Cognitive, Emotional, and Functional Outcomes in Trauma Intensive Care Unit Survivors Without Intracranial Hemorrhage. *The Journal of Trauma: Injury, Infection, and Critical Care*, *62*(1), 80–88. https://doi.org/10.1097/TA.0b013e31802ce9bd

Jackson, J., & Ely, E. (2013). Cognitive Impairment after Critical Illness: Etiologies, Risk Factors, and Future Directions. *Seminars in Respiratory and Critical Care Medicine*, *34*(02), 216–222. https://doi.org/10.1055/s-0033-1342984

Jones, C., Griffiths, R. D., Slater, T., Benjamin, K. S., & Wilson, S. (2006). Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Medicine*, *32*(6), 923–926. https://doi.org/10.1007/s00134-006-0112-y

Kachmar, A. G., Irving, S. Y., Connolly, C. A., & Curley, M. A. Q. (2018). A Systematic Review of Risk Factors Associated With Cognitive Impairment After Pediatric Critical Illness*. *Pediatric Critical Care Medicine*, *19*(3), e164–e171. https://doi.org/10.1097/PCC.0000000000001430

Kamdar, B. B., Needham, D. M., & Collop, N. A. (2012). Sleep deprivation in critical illness: its role in physical and psychological recovery. *Journal of Intensive Care Medicine*, *27*(2), 97–111. https://doi.org/10.1177/0885066610394322

Ketterer, M. W., Peltzer, J., Mossallam, U., Draus, C., Schairer, J., Rabbani, B., … Mccord, J. (2016). Cognitive impairment and reduced early readmissions in congestive heart failure. *Am J Accountable Care. Www. Ajmc. Com. Accessed*, *20*.

Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: a severity of disease classification system. *Crit Care Med*. https://doi.org/10.1097/00003246-198510000-00009

Kulkarni, A. P., & Agarwal, V. (2008). Extubation failure in intensive care unit: predictors and management. *Indian Journal of Critical Care Medicine : Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine*, *12*(1), 1–9. https://doi.org/10.4103/0972-5229.40942

Kwah, L. K., & Diong, J. (2014). National Institutes of Health Stroke Scale (NIHSS). *Journal of Physiotherapy*. https://doi.org/10.1016/j.jphys.2013.12.012

Lapinsky, S. E. (2015). Endotracheal intubation in the ICU. *Critical Care*, *19*(1), 258. https://doi.org/10.1186/s13054-015-0964-z

Larson, M. J., Weaver, L. K., & Hopkins, R. O. (2007). Cognitive sequelae in acute respiratory distress syndrome patients with and without recall of the intensive care unit. *Journal of the International Neuropsychological Society : JINS*, *13*(4), 595–605. https://doi.org/10.1017/S1355617707070749

Lee, K. H., Hui, K. P., Chan, T. B., Tan, W. C., & Lim, T. K. (1994). Rapid shallow breathing (frequency-tidal volume ratio) did not predict extubation outcome. *Chest*, *105*(2), 540–543. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8306759

Lioutas, V.-A., Hanafy, K. A., & Kumar, S. (2016). Predictors of extubation success in acute ischemic stroke patients. *Journal of the Neurological Sciences*, *368*, 191–194. https://doi.org/10.1016/j.jns.2016.07.017

Malhotra, S., Jordan, D., Shortliffe, E., & Patel, V. L. (2007). Workflow modeling in critical care: Piecing together your own puzzle. *Journal of Biomedical Informatics*, *40*(2), 81–92. https://doi.org/10.1016/J.JBI.2006.06.002

Marra, A., Ely, E. W., Pandharipande, P. P., & Patel, M. B. (2017). The ABCDEF Bundle in Critical Care. *Critical Care Clinics*, *33*(2), 225–243. https://doi.org/10.1016/j.ccc.2016.12.005

Marra, A., Pandharipande, P. P., Shotwell, M. S., Chandrasekhar, R., Girard, T. D., Shintani, A. K., … Vasilevskis, E. E. (2018). Acute Brain Dysfunction: Development and Validation of a Daily Prediction Model. *Chest*. https://doi.org/10.1016/J.CHEST.2018.03.013

Meade, M., Guyatt, G., Cook, D., Griffith, L., Sinuff, T., Kergl, C., … Epstein, S. (2001). Predicting success in weaning from mechanical ventilation. *Chest*, *120*(6 Suppl), 400S–24S. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11742961

Mehta, A. B., Syeda, S. N., Wiener, R. S., & Walkey, A. J. (2015). Epidemiological trends in invasive mechanical ventilation in the United States: A population-based study. *Journal of Critical Care*, *30*(6), 1217–1221. https://doi.org/10.1016/j.jcrc.2015.07.007

Mikkelsen, M. E., Christie, J. D., Lanken, P. N., Biester, R. C., Thompson, B. T., Bellamy, S. L., … Angus, D. C. (2012). The Adult Respiratory Distress Syndrome Cognitive Outcomes Study. *American Journal of Respiratory and Critical Care Medicine*, *185*(12), 1307–1315. https://doi.org/10.1164/rccm.201111-2025OC

Monsén, M. G., & Edéll-Gustafsson, U. M. (2005). Noise and sleep disturbance factors before and after implementation of a behavioural modification programme. *Intensive and Critical Care Nursing*, *21*(4), 208–219. https://doi.org/10.1016/J.ICCN.2004.12.002

Moon, K.-J., Jin, Y., Jin, T., & Lee, S.-M. (2018). Development and validation of an automated delirium risk assessment system (Auto-DelRAS) implemented in the electronic health record system. *International Journal of Nursing Studies*, *77*, 46–53. https://doi.org/10.1016/j.ijnurstu.2017.09.014

Needham, D. M., Bronskill, S. E., Calinawan, J. R., Sibbald, W. J., Pronovost, P. J., & Laupacis, A. (2005). Projected incidence of mechanical ventilation in Ontario to 2026: Preparing for the aging baby boomers. *Critical Care Medicine*, *33*(3), 574–579. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15753749

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., … Harvey, M. A. (2012). Improving long-term outcomes after discharge from intensive care unit. *Critical Care Medicine*, *40*(2), 502–509. https://doi.org/10.1097/CCM.0b013e318232da75

Pandharipande, P., Shintani, A., Peterson, J., Pun, B. T., Wilkinson, G. R., Dittus, R. S., … Ely, E. W. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*, *104*(1), 21–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16394685

Peitz, G. J., Balas, M. C., Olsen, K. M., Pun, B. T., & Ely, E. W. (2013). Top 10 Myths Regarding Sedation and Delirium in the ICU. *Critical Care Medicine*, *41*(9 Suppl 1), S46–S56. https://doi.org/10.1097/CCM.0b013e3182a168f5

Pisani, M. A., Araujo, K. L., Van Ness, P. H., Zhang, Y., Ely, E. W., & Inouye, S. K. (2006). A research algorithm to improve detection of delirium in the intensive care unit. *Critical Care*, *10*(4), R121. https://doi.org/10.1186/cc5027

Pulak, L. M., & Jensen, L. (2016). Sleep in the Intensive Care Unit. *Journal of Intensive Care Medicine*, *31*(1), 14–23. https://doi.org/10.1177/0885066614538749

Rogers, A. T., Bai, G., Lavin, R. A., & Anderson, G. F. (2017). Higher Hospital Spending on Occupational Therapy Is Associated With Lower Readmission Rates. *Medical Care Research and Review*, *74*(6), 668–686. https://doi.org/10.1177/1077558716666981

Roquilly, A., Cinotti, R., Jaber, S., Vourc'h, M., Pengam, F., Mahe, P. J., … Asehnoune, K. (2013). Implementation of an Evidence-based Extubation Readiness Bundle in 499 Brain-injured Patients. A Before–After Evaluation of a Quality Improvement Project. *American Journal of Respiratory and Critical Care Medicine*, *188*(8), 958–966. https://doi.org/10.1164/rccm.201301-0116OC

Rothenhäusler, H.-B., Ehrentraut, S., Stoll, C., Schelling, G., & Kapfhammer, H.-P. (2001). The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *General Hospital Psychiatry*, *23*(2), 90–96. https://doi.org/10.1016/S0163-8343(01)00123-2

Rowe, K., & Fletcher, S. (2008). Sedation in the intensive care unit. *Continuing Education in Anaesthesia Critical Care & Pain*, *8*(2), 50–55. https://doi.org/10.1093/bjaceaccp/mkn005

Sacanella, E., Pérez-Castejón, J. M., Nicolás, J. M., Masanés, F., Navarro, M., Castro, P., & López-Soto, A. (2011). Functional status and quality of life 12 months after discharge from a medical ICU in healthy elderly patients: a prospective observational study. *Critical Care*, *15*(2), R105. https://doi.org/10.1186/cc10121

Schmitz, R., Lantin, M., & White, A. (1998). Future needs in pulmonary and critical care medicine. *Cambridge, MA: Abt Associates*.

Semmler, A., Widmann, C. N., Okulla, T., Urbach, H., Kaiser, M., Widman, G., … Heneka, M. T. (2013). Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(1), 62–69. https://doi.org/10.1136/jnnp-2012-302883

Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K. A., … Elswick, R. K. (2002). The Richmond Agitation–Sedation Scale. *American Journal of Respiratory and Critical Care Medicine*, *166*(10), 1338–1344. https://doi.org/10.1164/rccm.2107138

Stanchina, M. L., Abu-Hijleh, M., Chaudhry, B. K., Carlisle, C. C., & Millman, R. P. (2005). The influence of white noise on sleep in subjects exposed to ICU noise. *Sleep Medicine*, *6*(5), 423–428. https://doi.org/10.1016/J.SLEEP.2004.12.004

Sternbach, G. L. (2000). The Glasgow Coma Scale. *The Journal of Emergency Medicine*. https://doi.org/10.1016/S0736-4679(00)00182-7

Suchyta, M. R., Jephson, A., & Hopkins, R. O. (2010). Neurologic Changes during Critical Illness: Brain Imaging Findings and Neurobehavioral Outcomes. *Brain Imaging and Behavior*, *4*(1), 22–34. https://doi.org/10.1007/s11682-009-9082-3

Sukantarat, K. T., Burgess, P. W., Williamson, R. C. N., & Brett, S. J. (2005). Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia*, *60*(9), 847–853.

https://doi.org/10.1111/j.1365-2044.2005.04148.x

The Society of Critical Care Medicine. (n.d.). Critical Care Statistics. Retrieved June 11, 2018, from http://www.sccm.org/Communications/Pages/CriticalCareStats.aspx

Thille, A. W., & Boissier, F. (2016). At the Critical Time of Deciding on Extubation, It Is Too Late to Assess Patient Breathlessness. *American Journal of Respiratory and Critical Care Medicine*, *193*(12), 1438–1439. https://doi.org/10.1164/rccm.201601-0187LE

Thille, A. W., Richard, J.-C. M., & Brochard, L. (2013). The Decision to Extubate in the Intensive Care Unit. *American Journal of Respiratory and Critical Care Medicine*, *187*(12), 1294–1302. https://doi.org/10.1164/rccm.201208-1523CI

Tobar, E., … T. G.-C., & 2009, undefined. (n.d.). HYPOACTIVE DELIRIUM IN SEPTIC MECHANICALLY VENTILATED PATIENT. PRELIMINARY DATA OF COGNITIVE AND PSYCHIATRIC FOLLOW UP. *LIPPINCOTT WILLIAMS & WILKINS …*. Retrieved from https://scholar.google.com/scholar?hl=en&as_sdt=0%2C22&q=Hypoactive+delirium+in+septic+mechanically+ventilated+patient.+Preliminary+data+of+cognitive+and+psychiatric+follow+up&btnG=

Tu, C.-S., Chang, C.-H., Chang, S.-C., Lee, C.-S., & Chang, C.-T. (2018). A Decision for Predicting Successful Extubation of Patients in Intensive Care Unit. *BioMed Research International*, *2018*, 1–11. https://doi.org/10.1155/2018/6820975

van den Boogaard, M., Pickkers, P., Slooter, A. J. C., Kuiper, M. A., Spronk, P. E., van der Voort, P. H. J., … Schoonhoven, L. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ (Clinical Research Ed.)*, *344*, e420. https://doi.org/10.1136/BMJ.E420

van den Boogaard, M., Schoonhoven, L., Maseda, E., Plowright, C., Jones, C., Luetz, A., … Pickkers, P. (2014). Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. *Intensive Care Medicine*, *40*(3), 361–369. https://doi.org/10.1007/s00134-013-3202-7

van Meenen, L. C. C., van Meenen, D. M. P., de Rooij, S. E., & ter Riet, G. (2014). Risk Prediction Models for Postoperative Delirium: A Systematic Review and Meta-Analysis. *Journal of the American Geriatrics Society*, *62*(12), 2383–2390. https://doi.org/10.1111/jgs.13138

Van Rompaey, B., Elseviers, M. M., Van Drom, W., Fromont, V., & Jorens, P. G. (2012). The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Critical Care*, *16*(3), R73. https://doi.org/10.1186/cc11330

Vasilevskis, E., Holtz, C., & Girard, T. (2015). The cost of delirium in the Intensive Care Unit: attributable costs of care intensity and mortality. *J Hosp Med*, *10*.

Venkataraman, S. T., Khan, N., & Brown, A. (2000). Validation of predictors of extubation success and failure in mechanically ventilated infants and children. *Critical Care Medicine*, *28*(8), 2991–2996. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10966284

Walder, B., Francioli, D., Meyer, J. J., Lançon, M., & Romand, J. A. (2000). Effects of guidelines implementation in a surgical intensive care unit to control nighttime light and noise levels. *Critical Care Medicine*, *28*(7), 2242–2247. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10921547

Wang, L.-H., Xu, D.-J., Wei, X.-J., Chang, H.-T., & Xu, G.-H. (2016). Electrolyte disorders and aging: risk factors for delirium in patients undergoing orthopedic surgeries. *BMC Psychiatry*, *16*(1), 418. https://doi.org/10.1186/s12888-016-1130-0

Wilcox, M. E., Brummel, N. E., Archer, K., Ely, E. W., Jackson, J. C., & Hopkins, R. O. (2013). Cognitive Dysfunction in ICU Patients. *Critical Care Medicine*, *41*, S81–S98. https://doi.org/10.1097/CCM.0b013e3182a16946

Woon, F. L., Dunn, C. B., & Hopkins, R. O. (2012). Predicting Cognitive Sequelae in Survivors of Critical Illness with Cognitive Screening Tests. *American Journal of Respiratory and Critical Care Medicine*, *186*(4), 333–340. https://doi.org/10.1164/rccm.201112-2261OC

Xie, H., Kang, J., & Mills, G. H. (2009). Clinical review: The impact of noise on patients' sleep and the effectiveness of noise reduction strategies in intensive care units. *Critical Care*, *13*(2), 208. https://doi.org/10.1186/cc7154

Zhang, Z., Chen, K., Ni, H., Zhang, X., & Fan, H. (2017). Sedation of mechanically ventilated adults in intensive care unit: a network meta-analysis. *Scientific Reports*, *7*(1), 44979. https://doi.org/10.1038/srep44979

Zieschang, T., Wolf, M., Vellappallil, T., Uhlmann, L., Oster, P., & Kopf, D. (2016). The Association of Hyponatremia, Risk of Confusional State, and Mortality. *Deutsches Arzteblatt International*, *113*(50), 855–862. https://doi.org/10.3238/arztebl.2016.0855

Zimmerman, J. E., Kramer, A. A., McNair, D. S., & Malila, F. M. (2006). Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Critical Care Medicine*. https://doi.org/10.1097/01.CCM.0000215112.84523.F0